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PRELIMINARY OBSERVATIONS ON URINARY OESTROGEN EXCRETION IN CERTAIN GYNAECOLOGICAL DISORDERS

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THE conservative therapy of functional gynaecological disorders does not at present rest on particularly strong foundations. A partial knowledge of the hormonal conditions existing in many of these disorders has been obtained by means of histological examination of the endometrium, by vaginal cytology or by means of semi-quantitative biological assays of blood and urine. It might be expected that a more complete knowledge of the hormonal production and excretion of the pituitary and ovarian glands would lead to a more rational approach in the treatment of these disorders.

Brown (1955a) published a chemical method of estimating the urinary oestrogens, oestriol, oestrone and oestradiol, with a proven degree of accuracy and later recorded the pattern of their excretion during the normal menstrual cycle (Brown, 1955b). The present paper is concerned with a preliminary survey of urinary oestrogen excretion in a variety of gynaecological disorders. In all, the results of investigation of 75 cases are presented and these represent our complete experience gained in this field up to the present time. This study, however, deals with one aspect only of the general problem, and other papers will follow from these departments in which measures of gonadotrophic and progestogenic function are also recorded.

The measurement of urinary oestrogens is an indirect method of measuring the amounts of oestrogens secreted in the body. It is well established that the ovaries and adrenals are the major sources of oestrogens in women and that the oestrogens they secrete are almost certainly oestradiol-17β and oestrone. These two oestrogens are inter-convertible in the body and are metabolized to a variety of conjugated products which are excreted largely in the urine. The urinary metabolites include the three "classical" oestrogens, oestriol, oestrone and oestradiol-17β, which are measured by the method employed, and also the more recently discovered oestrogens, such as 16-*epi*oestriol, 16α-hydroxyoestrone, 16β-hydroxyoestrone and 2-methoxyoestrone which are not measured by this method. The relative proportions of each of the metabolites excreted may vary from one individual to another, so that given levels of urinary oestriol, oestrone and oestradiol in different individuals may represent different levels of production of the primary hormones. This variability should be borne in mind in any attempt to correlate oestrogen production in the

body with levels found in the urine. In the work to be described, it has been found more significant to express results in terms of the sum of oestriol, oestrone and oestradiol, rather than of the individual oestrogens. It is likely that the measurement of all the urinary metabolites will give a much more exact picture of oestrogen production but this improvement must await further developments in assay techniques. It is unlikely, however, that the omission of these additional oestrogens in this study affects the general conclusions to any significant extent.

It is not proposed to review the previous literature on the quantitative excretion of oestrogens in gynaecological disorders. The methods of assay have been based largely on the vaginal cornification test introduced by Allen and Doisy in 1923 or later on the rat uterine weight method. The methods of assay used in the past have been subject to many gross errors and the sources of these have been fully reviewed by Loraine (1958).

Summary of Technique

(1) *Oestrogen Assay.* Urinary oestriol, oestrone and oestradiol-17β were measured by the method of Brown (1955a). In some cases, where interference by drugs was suspected or where the oestrogen levels were very low, the modified method described by Brown, Bulbrook and Greenwood (1957a) was used. In this work the term "total" oestrogens implies the sum of oestriol, oestrone and oestradiol. Results were not corrected for methodological losses.

(2) *Urinary Collection.* Sometimes 24-hours specimens of urine were collected by the nursing staff while the patient was in hospital; more frequently the urine was collected most conscientiously by the patient herself in her own home. On occasions, pressure of work made it necessary to pool the urine in 48-hours samples. The results are expressed in terms of 24-hours urinary excretion.

(3) *Endometrial Histology.* Sections of the endometrium were stained by haematoxylin and eosin and, on occasion, stains were used to demonstrate glycogen and mucin. Before this paper was written, all the sections involved were gathered together and a fresh report written without any reference to the clinical notes. These new reports were then reviewed in conjunction with the menstrual data and the oestrogen excretion values.

The results are presented in the following sections:

I. Post-menopausal bleeding.

II. Dysfunctional uterine bleeding.

III. Amenorrhoea.

The Normal Menstrual Cycle

Before embarking upon a description of oestrogen excretion in abnormal states, it will be useful to review the knowledge on oestrogen excretion in the normal menstrual cycle. During the first 2 or 3 days of bleeding in a 28-day cycle the oestrogen excretion is low, being in the range 4–22 μg. "total" oestrogen per day (mean 12 μg.). The oestrogen levels then rise to a well-defined peak which occurs on about the 13th day of the cycle. This peak has been called the "ovulatory" or "follicular" maximum. The oestrogen excretion at this time ranges from 35–100 μg. (mean 57 μg.) per 24 hours. The characteristic features of this peak are that it is shown by all 3 oestrogens, the rise to the peak is usually gradual and the subsequent fall is often abrupt, the interval of time between the peak and the onset of menstruation is usually about 14 days, the rise and fall of the oestriol levels tend to lag behind the rise and fall of the oestrone and oestradiol levels.

Following this temporary elevation, there is a short period of decrease followed by another rise, termed the "luteal" maximum, which averages about 33 μg. daily (range 17–87 μg.). In most cycles studied, the follicular maximum exceeds that of the luteal maximum but this is not invariable. During the last few days of the cycle, the oestrogen excretion falls rapidly and by the first day of the next cycle it has again reached an average figure of 12 μg. daily. It is important that this pattern and these mean excretion rates should be remembered when considering abnormalities of the cycle. Figure 1 illustrates the values found during normal ovulatory menstrual cycles.

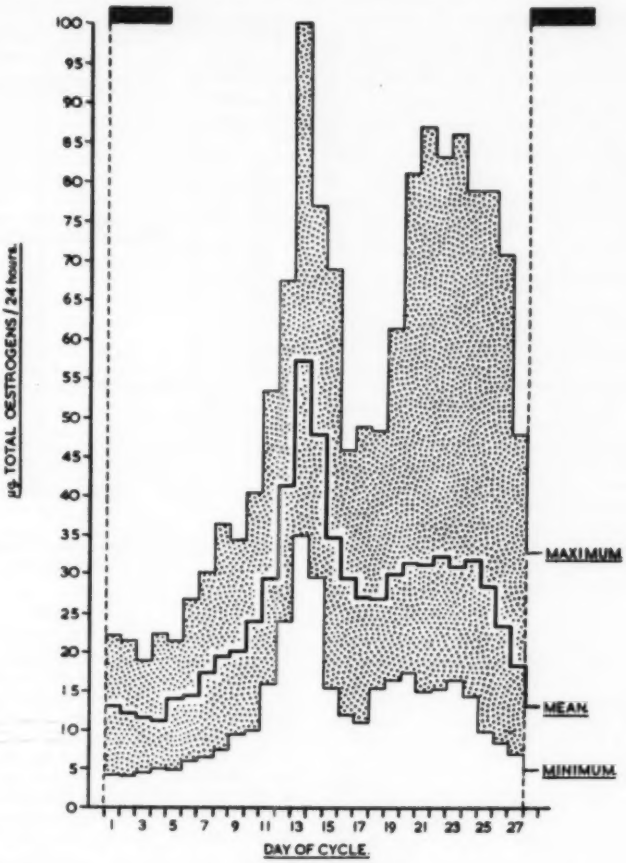

FIG. 1

Mean, maximum and minimum levels of total urinary oestrogens from 16 women, aged 18–41 years, with normal menstrual cycles. Time between onset of bleeding (day 1) and ovulatory peak of oestrone/oestradiol varied from 10 to 18 days (mean 13 days) and, between oestrone/oestradiol ovulatory peak and first day of next menstruation, from 12 to 16 days (mean 14 days). Curves were constructed by superimposing individual curves in such a way that each of the oestrone/oestradiol ovulatory peaks coincide with day 13 of the composite curves.
(■■■ = Menstruation)

SECTION I

POST-MENOPAUSAL HAEMORRHAGE

This section consists of 23 patients in whom the presenting symptom was post-menopausal haemorrhage. In these cases there was a wide variation in the interval between menopause and bleeding and a variety of pathological conditions were responsible for the bleeding. For the purposes of this study it is convenient to subdivide the cases into 3 groups according to the histological state of the endometrium.

Group I. Inactive Endometrium

In the 10 cases comprising this group, inactivity of the endometrium was determined in the following circumstances: curettage was performed and tissue was obtained showing the accepted histological picture of a senile endometrium; curettage was performed but no endometrial tissue could be obtained; in cases of adenocarcinoma of the endometrium or endometrial polypus no normal endometrial tissue was obtained on curettage.

Case No. 1. Aged 61 years. Para 1+1. The menopause occurred at 55 years and 5½ years later there was a recurrence of bleeding which lasted for 3 months prior to admission. Diagnostic curettage performed on 1st November, 1955 provided the diagnosis of adenocarcinoma of the endometrium and hysterectomy with bilateral salpingo-oöphorectomy was carried out on 28th November, 1955. No normal endometrium was discovered in either the curettage or hysterectomy specimens. *Oestrogen Assays:* 2×48 hours urinary collections were made in the immediate pre-operative period. Range: oestriol 2·1 μg., 5·0 μg. (mean 3·5 μg.); oestrone 0·7 μg., 1·9 μg. (mean 1·3 μg.); oestradiol 1·1 μg., 1·2 μg. (mean 1·2 μg.); total 3·9 μg., 8·1 μg. (mean 6·0 μg.).

Case No. 2. Aged 63 years. Para 5+0. The menopause occurred at 52 years and 11 years later there was bleeding for 6 weeks prior to admission. On examination there was found to be a marked degree of genital prolapse with cervical ulceration and senile vaginitis. Diagnostic curettage performed on 30th December, 1955 failed to obtain any endometrial tissue. Pelvic floor repair was effected but the uterus was not removed. *Oestrogen Assays:* 1×24 hours and 1×48 hours urinary collections were made immediately prior to operation. Range: oestriol 2·4 μg., 3·7 μg. (mean 3·3 μg.); oestrone nil, 0·5 μg. (mean 0·3 μg.); oestradiol nil, nil (mean nil); total 2·4 μg., 4·2 μg. (mean 3·6 μg.).

Case No. 3. Aged 56 years. Para 1+0. The menopause occurred at 50 years and, following 6-years amenorrhoea, there was bleeding for 5 months prior to admission. Diagnostic curettage was carried out on 1st February, 1956 and provided the diagnosis of endometrial adenocarcinoma. No normal endometrium was demonstrated in the curettings. This case was treated by radium. *Oestrogen Assays:* 3×24 hours urinary collections were made following the curettage. Range: oestriol 3·1 μg. to 6·6 μg. (mean 5·1 μg.); oestrone 1·2 μg. to 1·9 μg. (mean 1·4 μg.); oestradiol nil to 2·2 μg. (mean 0·7 μg.); total 4·3 μg. to 9·7 μg. (mean 7·2 μg.).

Case No. 4 (Fig. 2). Aged 72 years. Para 0+0. The menopause occurred at 42 years and 21 years later bleeding occurred and continued intermittently for 9 years until admission. Diagnostic curettage on 19th April, 1956 supplied the diagnosis of endometrial adenocarcinoma and hysterectomy with bilateral salpingo-oöphorectomy was carried out on 26th April, 1956. In the hysterectomy specimen areas of normal senile endometrium were demonstrated. *Oestrogen Assays:* 4×24 hours urinary collections were made prior to hysterectomy. Range: oestriol 1·3 μg. to 3·4 μg. (mean 2·3 μg.); oestrone 0·8 μg. to 1·3 μg. (mean 0·9 μg.); oestradiol nil to nil (mean nil); total 2·1 μg. to 4·7 μg. (mean 3·2 μg.). Two×24 hours urinary collections were made following hysterectomy. Range: oestriol 1·3 μg., 4·0 μg. (mean 2·7 μg.); oestrone nil, 0·7 μg. (mean 0·4 μg.); oestradiol nil, nil (mean nil); total 2·0 μg., 4·0 μg. (mean 3·0 μg.).

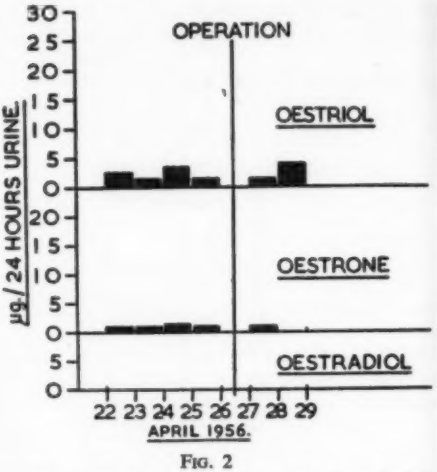

FIG. 2

Case No. 4. Post-menopausal bleeding. Endometrial adenocarcinoma.

Case No. 5. Aged 58 years. Para 5+0. The menopause occurred at 46 years. There followed a period of amenorrhoea of 12 years and then 8-months bleeding before admission for oestrogen assays. Diagnostic curettage performed on 7th May, 1956 revealed a senile endometrium. *Oestrogen Assays:* 5×24 hours urinary collections were made immediately prior to curettage. Range: oestriol 1·1 μg. to 2·9 μg. (mean 2·2 μg.); oestrone 1·3 μg. to 1·8 μg. (mean 1·5 μg.); oestradiol nil to nil (mean nil); total 2·7 μg. to 4·7 μg. (mean 3·8 μg.).

In the follow-up of this case further episodes of bleeding occurred but were considered to be due to a vascular urethral caruncle and another curettage performed on 26th April, 1957 again demonstrated senile endometrium.

Case No. 6. Aged 61 years. Para 1+0. The menopause occurred at 38 years and was followed by amenorrhoea for 23 years. Intermittent vaginal bleeding occurred for one year prior to admission. Diagnostic curettage was performed on 8th June, 1956 and provided the diagnosis of endometrial adenocarcinoma. Treatment by hysterectomy with bilateral salpingo-oöphorectomy was carried out on 16th June, 1956. Examination of the extirpated uterus confirmed the presence of adenocarcinoma but areas of endometrium adjacent to the tumour showed characteristic senile atrophic changes. *Oestrogen Assays:* 4×24 hours urinary collections were made prior to laparotomy. Range: oestriol 4·2 μg. to 10·2 μg. (mean 7·5 μg.); oestrone 1·0 μg. to 1·8 μg. (mean 1·5 μg.); oestradiol nil to nil (mean nil); total 5·2 μg. to 12·0 μg. (mean 9·0 μg.).

Case No. 7. Aged 54 years. Para 0+0. The menopause occurred at 50 years and 4 years later there was vaginal bleeding for one week prior to admission. On examination there was found to be a vascular polypus arising from the cervix and this was excised on 13th November, 1956. At the same time curettage was carried out but no endometrial tissue was obtained. It was accepted that the cervical polypus was the source of bleeding and there was no recurrence of this symptom during the subsequent follow-up period. *Oestrogen Assays:* 2×48 hours urinary collections were made prior to operation. Range: oestriol 2·2 μg., 4·1 μg. (mean 3·1 μg.); oestrone 1·6 μg., 1·4 μg. (mean 1·5 μg.); oestradiol nil, nil (mean nil); total 3·8 μg., 5·5 μg. (mean 4·6 μg.).

Case No. 8. Aged 57 years. Para 8+0. The menopause was induced by intra-uterine radium at the age of 55 years. The indication was metropathia haemorrhagica. Following amenorrhoea for 2 years intermittent vaginal bleeding occurred during the 2 months prior to admission. No abnormality could be discovered upon examination and diagnostic curettage on 3rd November, 1956 produced only scant specimens of senile endometrium. Hysterectomy with bilateral salpingo-oöphorectomy was carried out on 17th November, 1956 and examination of the uterus again revealed normal senile endometrium. No adequate explanation for the bleeding could be determined. *Oestrogen Assays:* 6×48 hours urinary collections were made prior to laparotomy. Range: oestriol 2·9 μg. to 6·2 μg. (mean 4·1 μg.); oestrone 1·7 μg. to 2·9 μg. (mean 2·4 μg.); oestradiol nil to 3·7 μg. (mean 1·4 μg.); total 4·9 μg. to 12·4 μg. (mean 7·9 μg.).

Case No. 9. Aged 64 years. Para 4+0. The menopause occurred at 53 years. Following 11 years of amenorrhoea there was vaginal bleeding for 16 days prior to admission. The diagnosis of adenocarcinoma of the uterus was made as a result of diagnostic curettage on 4th February, 1957 but in the endometrial tissue examined there was no demonstrable normal endometrium. Treatment, which was by radium, was commenced on 15th April, 1957. *Oestrogen Assays:* only 1×24 hours urinary collection was made prior to the commencement of treatment. Results: oestriol 5·2 μg.; oestrone 0·7 μg.; oestradiol nil; total 5·9 μg.

Case No. 10. Aged 70 years. Para 0+0. The menopause occurred at 46 years. After a period of amenorrhoea lasting for 24 years there was vaginal bleeding for one week prior to admission. No abnormality could be detected upon examination. At diagnostic curettage on 27th February, 1957 two endometrial polypi were removed but the remainder of the endometrium was atrophic. During the follow-up period there was no recurrence of bleeding. *Oestrogen Assays:* only 1×48 hours urinary collection was made following curettage. Results: oestriol 2·9 μg.; oestrone 1·4 μg.; oestradiol nil; total 4·3 μg.

In this group of cases there was no evidence, either clinically or histologically, of oestrogenic stimulation. In patients Nos. 1, 3, 4, 6 and 9, the cause of the post-menopausal bleeding was established as being due to adenocarcinoma of the body of the uterus; in Case No. 2 to cervical ulceration; in Case No. 7 to a cervical polypus; and in Case No. 10 to localized endometrial polypi. The origin of bleeding was not determined in Cases Nos. 5 and 8. It can be assumed, therefore, that from the point of view of ovarian function, all cases in this group come within the category of normally post-menopausal patients. An analysis of the mean figures obtained in each of these 10 cases gave the following results: actual range: oestriol 2·2 μg. to 7·5 μg. (mean 3·9 μg. ±1·6 μg.*); oestrone 0·3 μg. to 2·4 μg. (mean 1·3 μg.±0·6 μg.*); oestradiol nil to 1·4 μg. (mean 0·3 μg.±0·5 μg.*); total 3·2 μg. to 9·0 μg. (mean 5·5 μg.±2·0 μg.*). These figures can be regarded as representative of the normal post-menopausal woman with an atrophic endometrium. They represent oestrogen levels which are insufficient to stimulate growth of the endometrium. These oestrogens are not of ovarian origin since bilateral oöphorectomy (example Case No. 4) has no effect on the amounts produced. They are probably derived from the adrenal cortex. These values are very similar to those already reported for post-menopausal women (McBride, 1957; Brown, 1958; Loraine, 1958).

Group II. Endometrium not *Investigated*

In this group of 6 cases the cause of post-menopausal bleeding was well-established carcinoma of the cervix. In the investigation of these

* Standard deviation.

cases endometrial curettage was not carried out so that no histological evidence on the state of the endometrium was available.

Case No. 11. Aged 64 years. Para 11+0. The menopause occurred at 50 years and 14 years later there was vaginal bleeding for 9 months prior to admission. The diagnosis of squamous epithelioma of the cervix was established. *Oestrogen Assays:* 4×24 hours urinary collections were made before treatment by radium was instituted in February, 1956. Range: oestriol 2·8 μg. to 5·4 μg. (mean 4·1 μg.); oestrone 2·3 μg. to 4·1 μg. (mean 3·1 μg.); oestradiol 1·4 μg. to 2·9 μg. (mean 1·7 μg.); total 7·4 μg. to 10·9 μg. (mean 8·9 μg.).

Case No. 12. Aged 60 years. Para 5+0. The menopause occurred at 48 years and was followed by 12-years amenorrhoea. Vaginal bleeding for 10 weeks took place prior to admission. The diagnosis of squamous epithelioma of the cervix was established. *Oestrogen Assays:* 2×24 hours urinary collections were made before treatment by radium was commenced in March, 1956. Range: oestriol 2·0 μg., 2·7 μg. (mean 2·4 μg.); oestrone 0·7 μg., 1·9 μg. (mean 1·3 μg.); oestradiol nil, 1·3 μg. (mean 0·6 μg.); total 2·7 μg., 5·9 μg. (mean 4·3 μg.).

Case No. 13. Aged 59 years. Para 12+0. The menopause took place at 49 years. Amenorrhoea for 10 years preceded 6-weeks vaginal bleeding which continued until admission. The diagnosis of squamous epithelioma of the cervix was established. *Oestrogen Assays:* 2×24 hours urinary collections were made before treatment by radium was commenced in April, 1956. Range: oestriol 2·0 μg., 4·4 μg. (mean 3·2 μg.); oestrone 0·9 μg., 1·0 μg. (mean 0·9 μg.); oestradiol nil, nil (mean nil); total 2·9 μg., 5·4 μg. (mean 4·1 μg.).

Case No. 14. Aged 64 years. Para 4+0. The menopause occurred at the early age of 34 years and was followed by amenorrhoea for 30 years. Intermittent vaginal bleeding was present for 6 months prior to admission when the diagnosis of squamous epithelioma of the cervix was established. *Oestrogen Assays:* 5×24 hours urinary collections were made before treatment by radium was commenced in April, 1956. Range: oestriol nil to 3·5 μg. (mean 2·0 μg.); oestrone 1·3 μg. to 2·4 μg. (mean 1·6 μg.); oestradiol nil to nil (mean nil); total 2·4 μg. to 5·1 μg. (mean 3·6 μg.).

Case No. 15. Aged 66 years. Para 6+0. The menopause occurred at 42 years. Amenorrhoea was interrupted after 24 years by vaginal bleeding which continued intermittently for 4 months until admission when the diagnosis of squamous epithelioma of the cervix was established. *Oestrogen Assays:* 2×48 hours urinary collections were made before treatment by radium was undertaken in November, 1956. Range: oestriol 2·2 μg., 4·1 μg. (mean 3·1 μg.); oestrone 1·2 μg., 1·6 μg. (mean 1·4 μg.); oestradiol nil, nil (mean nil); total 3·8 μg., 5·3 μg. (mean 4·5 μg.).

Case No. 16. Aged 62 years. Para 0+0. In this unmarried patient the menopause was induced by intrauterine radium at the age of 55 years on account of metropathia haemorrhagica. Three years later an episode of bleeding occurred following oestrogen therapy and curettage at that time produced endometrium showing cystic hyperplasia. There was no further bleeding for 4 years when there was a recurrence at 62 years. On this occasion the bleeding lasted for 4 weeks until admission when the diagnosis of cervical adenocarcinoma was established. *Oestrogen Assays:* 2×48 hours urinary collections were made prior to the commencement of treatment by radium in March, 1957. Range: oestriol 4·2 μg., 9·0 μg. (mean 6·6 μg.); oestrone 1·1 μg., 1·7 μg. (mean 1·4 μg.); oestradiol nil, nil (mean nil); total 5·9 μg., 10·1 μg. (mean 8·0 μg.).

In the 6 patients comprising this group a total of 17 urinary oestrogen assays were made. An analysis of the results gave the following figures for the group: Range: oestriol 2·0 μg. to 6·6 μg. (mean 3·6 μg. ±1·7 μg.*); oestrone 0·9 μg. to 3·1 μg. (mean 1·6 μg. ±0·8 μg.*); oestradiol nil to 1·7 μg. (mean 0·4 μg. ±0·7 μg.*); total 3·6 μg. to 8·9 μg. (mean 5·6 μg. ±2·3 μg.*). These figures are closely similar to those obtained in Group I. Thus it would be reasonable to conclude that the patients of this group were, from the point of view of ovarian function, normally post-menopausal.

Group III. Active Endometrium

In this group of 7 cases diagnostic curettage produced evidence of active endometrium showing varying degrees of oestrogenic stimulation. In all cases it seemed certain that the endometrium was the site of haemorrhage as no other cause of bleeding was discovered.

Case No. 17. Aged 60 years. Para 7+1. The menopause occurred at 50 years. Amenorrhoea continued for 10 years and was followed by 5-months bleeding. Endometrium obtained by curettage on 1st December, 1955 showed cystic glandular hyperplasia. Hysterectomy with bilateral salpingo-oöphorectomy was performed on 9th December, 1955 and the specimen again showed cystic glandular hyperplasia of the endometrium. No pathological features were noted in the ovaries. *Oestrogen Assays:* 2×48 hours pre-operative urinary collections were made. Range: oestriol 8·4 μg., 13·8 μg. (mean 11·1 μg.); oestrone 2·0 μg., 2·9 μg. (mean 2·5 μg.); oestradiol nil, nil (mean nil); total 10·4 μg., 16·7 μg. (mean 13·6 μg.). Two×48 hours post-operative collections were made. Range: oestriol 3·6 μg., 3·8 μg. (mean

* Standard deviation.

3·7 μg.); oestrone 0·6 μg., 0·7 μg. (mean 0·7 μg.); oestradiol nil, nil (mean nil); total 4·3 μg., 4·5 μg. (mean 4·4 μg.).

Case No. 18. Aged 60 years. Para 6+2. The menopause occurred at 53 years and 7 years later there was uterine bleeding which continued for 10 days prior to admission. On examination a uterine fibroid was palpated. Diagnostic curettage performed on 27th January, 1956 produced fragments of atrophic endometrium. Vaginal hysterectomy without removal of appendages was carried out on 10th February, 1956 and examination of the specimen showed a submucous fibroid and scattered early proliferative changes in the endometrium. *Oestrogen Assays:* 4×24 hours pre-operative urinary collections were made. Range: oestriol 4·6 μg. to 7·9 μg. (mean 6·2 μg.); oestrone 2·2 μg. to 2·9 μg. (mean 2·6 μg.); oestradiol nil to 1·4 μg. (mean 0·3 μg.); total 7·6 μg. to 10·8 μg. (mean 9·1 μg.).

Case No. 19. Aged 46 years. Para 3+0. The artificial menopause was induced by intra-uterine radium at 42 years. Uterine bleeding, lasting for 2 weeks, occurred at 44 years and again, prior to admission, for 4 days at 46 years. On examination no pelvic abnormality was detected and diagnostic curettage performed on 9th February, 1956 produced endometrium showing early proliferative changes. *Oestrogen Assays:* 4×24 hours pre-operative urinary collections were made. Range: oestriol 1·9 μg. to 4·5 μg. (mean 3·0 μg.); oestrone 1·1 μg. to 2·3 μg. (mean 1·8 μg.); oestradiol nil to 1·6 μg. (mean 0·8 μg.); total 3·5 μg. to 8·2 μg. (mean 5·6 μg.). Follow-up: from 46 to 47 years regular monthly bleedings occurred over a period of 9 months, thereafter there was total amenorrhoea.

Case No. 20 (Fig. 3). Aged 56 years. Para 3+0. The menopause occurred at 51 years and 5 years later there was an episode of bleeding lasting for 6 weeks before admission. Examination provided the diagnosis of ovarian tumour and on 16th March, 1956 this was removed together with the uterus and contralateral appendages. The specimen showed cystic glandular hyperplasia of the endometrium and a benign ovarian pseudomucinous cystadenoma. *Oestrogen Assays:* 2×48 hours and 1×24 hours pre-operative collections were made. Range: oestriol 19·8 μg. to 28·8 μg. (mean 27·1 μg.); oestrone 9·6 μg. to 18·6 μg. (mean 15·4 μg.); oestradiol 1·7 μg. to 2·5 μg. (mean 2·0 μg.); total 31·1 μg. to 49·9 μg. (mean 44·0 μg.). Three×24 hours post-operative collections were made. Values fell from oestriol 10·6 μg. to 4·3 μg.; oestrone 6·2 μg. to 0·8 μg.; oestradiol 0·5 μg. to nil; total 17·0 μg. to 5·8 μg.

Case No. 21. Aged 68 years. Para 0+0. The menopause occurred at 43 years and following 25-years amenorrhoea there was 3-months bleeding prior to admission. Examination revealed an ovarian tumour and on 25th October, 1956 this was removed together with the uterus. The specimen showed an early proliferative pattern in the endometrium and adenocarcinoma of the ovary. *Oestrogen Assays:* 2×48 hours pre-operative

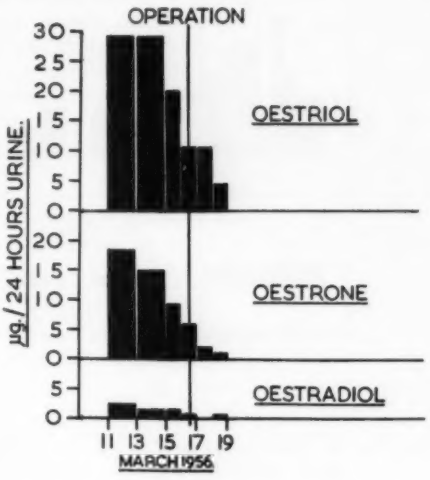

FIG. 3

Case No. 20. Post-menopausal bleeding. Benign ovarian pseudomucinous cystadenoma.

collections were made. Range: oestriol 5·7 μg., 12·0 μg. (mean 8·9 μg.); oestrone 3·5 μg., 6·0 ug. (mean 4·8 μg.); oestradiol nil, nil (mean nil); total 9·2 μg., 18·0 μg. (mean 13·6 μg.).

Case No. 22. Aged 47 years. Para 0+0. The menopause occurred at 40 years and, after 7-years amenorrhoea, there was bleeding for 6 weeks prior to admission. Right ovariotomy had been carried out in 1933. Endometrium obtained by curettage on 8th November, 1956 showed cystic glandular hyperplasia. Hysterectomy with left salpingo-oöphorectomy was performed on 20th May, 1957 and the specimen again showed cystic glandular hyperplasia of the endometrium. There were no pathological features in the ovary. *Oestrogen Assays:* 1×48 hours immediate pre-operative collections was made. Results: oestriol 1·2 μg.; oestrone 1·4 μg.; oestradiol nil; total 2·6 μg.

Case No. 23 (Fig. 4). Aged 77 years. Para 2+0. The menopause occurred at 47 years and, following 30 years amenorrhoea, there was an episode of bleeding lasting for 3 weeks prior to admission. Examination revealed an ovarian tumour and this was removed together with the uterus and opposite appendages on 17th October, 1957. The specimen showed cystic glandular hyperplasia of the endometrium and a combined granulosal and thecal celled tumour of the ovary. *Oestrogen Assays:* 7×24

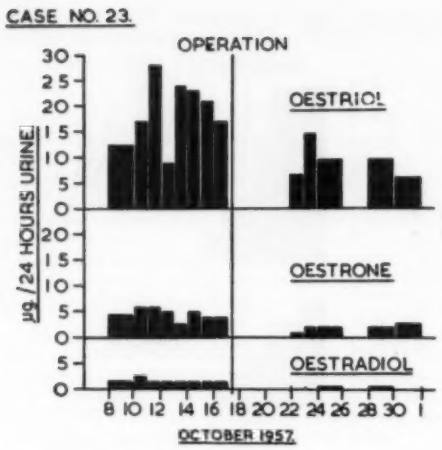

FIG. 4

Case No. 23. Post-menopausal bleeding. Functioning ovarian tumour.

hours and 1×48 hours immediate pre-operative collections were made. Range: oestriol 9·2 μg. to 28·8 μg. (mean 19·0 μg. ±6·4 μg.*); oestrone 2·7 μg. to 5·9 μg. (mean 4·5 μg. ±1·1 μg.*); oestradiol 1·4 μg. to 2·5 μg. (mean 1·8 μg. ±0·3 μg.*); total 15·7 μg. to 36·3 μg. (mean 25·3 μg. ±6·4 μg.*). Two×24 hours and 3×48 hours post-operative collections were made. Range: oestriol 6·0 μg. to 14·0 μg. (mean 8·8 μg.); oestrone 0·9 μg. to 2·6 μg. (mean 2·0 μg.); oestradiol nil to 0·7 μg. (mean 0·3 μg.); total 7·4 μg. to 16·2 μg. (mean 11·1 μg.).

In each of the 7 cases in this group, with a history of post-menopausal bleeding, examination of the endometrium demonstrated histological changes consistent with oestrogenic stimulation of a varying degree. In Cases Nos. 17, 20, 22 and 23 there was cystic glandular hyperplasia, an endometrial pattern usually associated with the clinical condition of Metropathia Haemorrhagica. In the other 3 cases, Nos. 18, 19 and 21, early proliferative changes of the endometrium were found. From the purely histological point of view, the interpretation must be that there was an adequate level of circulating oestrogens to cause endometrial stimulation and that the endometrium was sufficiently responsive to show the effects of such stimulation. In not all of the cases was it possible to demonstrate an ovarian origin of oestrogen output. In Case No. 17 there were no recognizable pathological features in the ovaries; in Case No. 18 the ovaries were not available for examination; in Case No. 19 there was almost certainly a revival of ovarian function following inadequate radiotherapy; in Case No. 20 there was a benign ovarian pseudomucinous cystadenoma and it is reasonable to suppose that the origin of oestrogens in this case was functioning stroma within the tumour; in Case No. 21 there was an ovarian adenocarcinoma and the same observation can be applied to this case as in Case No. 20; in Case No. 22 there were no pathological features in the ovary; in Case No. 23 there was a functioning tumour which was clearly the source of oestrogens.

Three of the cases showing cystic glandular hyperplasia, Cases Nos. 17, 20 and 23, excreted larger amounts of oestrogens (the average "total" excretions for each individual were 13·6 μg., 44·0 μg. and 25·3 μg. per 24 hours respectively) than the post-menopausal cases of groups I and II who showed no evidence of endometrial stimulation (the highest figure found in these groups was 12·4 μg. per 24 hours). In each of these cases the urinary oestrogen levels decreased following bilateral oöphorectomy. A single observation made on the other case with cystic glandular hyperplasia (Case No. 22) showed that the amounts of oestrogens excreted were within the range where stimulation of the endometrium would not have been expected. This apparent anomaly will be discussed under Section II, Group II.

In the 3 cases, Nos. 18, 19 and 21, which showed early proliferative changes only, the average total oestrogen excretions were 9·1 μg., 5·6 μg., and 13·6 μg. per 24 hours respectively. Excretion of 9·1 μg. total oestrogens per 24 hours is in the upper limits of the range found in groups I and II in whom no endometrial stimulation occurred: 5·6 μg. is well within, and 13·6 μg. is just above, this range. The significance of this apparent discrepancy in results will be referred to in the general discussion.

* Standard deviation.

Section II

Dysfunctional Uterine Bleeding

It is not proposed to enter into any detailed discussion of this very confused subject. The terminology is chaotic and there are few textbooks either in general gynaecology or in endocrinology which describe the condition in even remotely similar terms. By dysfunctional uterine bleeding we mean a condition of irregular or excessive menstruation which is not due to any obvious disease in the genital tract. Although the majority of cases occur towards the end of reproductive life, it is well known that some cases occur in adolescence, and perhaps a third occurs during the intervening years.

The simplest form of dysfunctional uterine bleeding is the anovulatory cycle. Here the menstrual disturbance is minimal or absent, and the episodes of anovulatory menstruation are frequently discovered only when pre-menstrual biopsies of the endometrium are taken during investigation of infertility. Most cases of dysfunctional bleeding, however, do suffer from irregular and excessive menstruation. The classical type of dysfunctional uterine bleeding is "metropathia haemorrhagica" or "dysfunctional bleeding associated with cystic glandular hyperplasia of the endometrium". Such cases are readily recognized both clinically and pathologically and are explained as being due to failure of ovulation and formation of a corpus luteum, associated with prolonged oestrogenic stimulation of the endometrium. Uterine bleeding in these women has been thought to be due to a sudden fall in oestrogen production with consequent disintegration of the endometrium. It has also been suggested that the bleeding might on occasion be due to necrosis in the endometrial polypi which are present so often and which have outgrown their blood supply. The precise role of the spiral arterioles in the mechanism of bleeding in this type of case remains obscure.

There are, however, a very large number of cases of dysfunctional uterine haemorrhage which do not present the well-known features of cystic glandular hyperplasia and, indeed, examination of the endometrium in these women shows that this may be in any stage ranging from a "resting", almost atrophic, endometrium to one that is in active proliferation. These cases have usually been ascribed to persistent failure of ovulation and corpus luteum function leading to a prolonged but often weak oestrogenic stimulus to the endometrium. There are, however, some cases in which it is clear that a corpus luteum has been formed but its progestogenic activity has been weak and conditions of "irregular ripening" or "irregular shedding" of the endometrium have been described.

The results of this study will be presented under the following headings:

(1) Anovulatory cycles.

(2) Cystic glandular hyperplasia (metropathia haemorrhagica).

(3) Other forms of dysfunctional uterine bleeding.

Group I. Anovulatory Menstrual Cycles

For the purposes of this paper, anovulatory menstrual cycles are defined as more or less regular monthly episodes of bleeding originating from endometria which are in the proliferative phase and show no signs of secretory activity.

It has not been easy to obtain complete oestrogen excretion data in individuals exhibiting such cycles. Four cases, Nos. 24, 25, 26 and 27, falling within this group have been adequately studied for periods of time which include at least 2 phases of menstrual bleeding. Three of these exhibited ovulatory as well as anovulatory cycles during the study. Diagnosis of ovulatory and anovulatory cycles was based on endometrial biopsies performed at about the time of onset of bleeding.

Case No. 24 (Fig. 5). Aged 19 years. Para 0+0. From the menarche at 14 years this patient had a long history of bleeding which occurred at intervals of one to 3 months and lasted up to 16 days. Her menstrual history in the months before oestrogen assays were undertaken was as follows: bleeding occurred on 10th September, 1954 and lasted until the 26th when she was subjected to a curettage. Further episodes of bleeding occurred on 20th November, 1954 and 20th January, 1955 when urine collections were commenced. Figure 5 shows the results obtained during January, February and March, 1955. The bleeding commencing on 15th February lasted 13 days and that commencing on 21st March, 5 days. Endometrial biopsies performed on 28th January

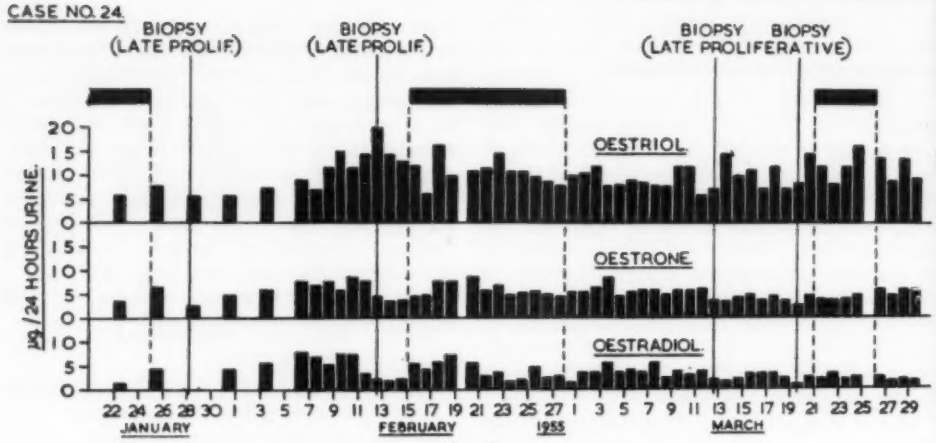

FIG. 5

Case No. 24. Anovulatory menstruation.

and before the February and March bleedings showed a late proliferative endometrium. A further biopsy performed on the first day of a menstrual period commencing on 14th April (not illustrated) was also of this type. It can therefore be concluded that all these bleeding phases were anovulatory in nature. It is seen that, apart from the usual day-to-day variations, the urinary oestrogen levels remained more or less constant especially during the latter half of the investigation. There was no rise resembling the mid-cycle peak of an ovulatory menstrual cycle, nor a fall in oestrogen excretion prior to menstruation. The amounts excreted were maintained at approximately 10 µg. oestriol, 5 µg. oestrone and 3 µg. oestradiol, or a total of 18 µg. per 24-hours urine.

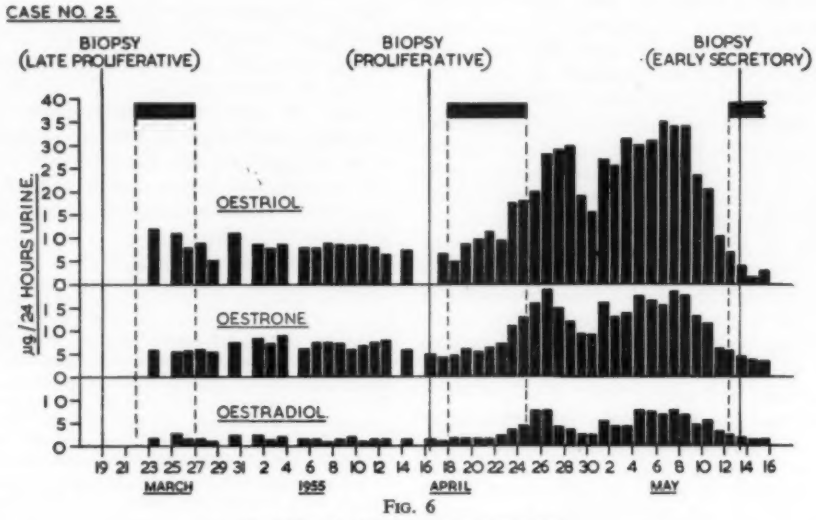

FIG. 6

Case No. 25. Anovulatory menstruation.

Case No. 25 (Fig. 6). Aged 26 years. Para 0+0. From the onset of menstruation at 13 years, this patient's menstrual history was one of great irregularity. Menstrual losses occurred at intervals of one to several months, the duration of the loss varying from a few days to 5 weeks.

An endometrial biopsy performed on 19th March, 1955 showed a late proliferative endometrium. Bleeding commenced on 22nd March and lasted 5 days. Further episodes of bleeding commenced on 18th April and 12th May. A biopsy taken just before the April bleeding revealed a late proliferative endometrium but that taken just after the onset of the May bleeding showed a secretory endometrium with a rather weak luteal reaction.

Figure 6 shows the oestrogen excretion measured throughout this period. For approximately a month before the onset of anovulatory bleeding on 18th April, the daily excretion remained at approximately 17 μg. total oestrogens per 24-hours urine. From 18th March to 12th May the picture changed completely to that of an ovulatory cycle with a shortened follicular phase. It is of interest to record that this patient became pregnant during the subsequent cycle.

Case No. 26 (Fig. 7). Aged 16 years. Para 0+0. Menstruation commenced at the age of 12 years and was regular until recently when menstrual periods became irregular. A bleeding phase commencing on 11th March, 1956 had lasted until 10th April. Urinary oestrogens were measured from 7th April through the month of May until 14th June. During this time she had 3 episodes of bleeding: 29th April to 3rd May; 19th May to 24th May; and 8th June to 14th June. Endometrial biopsies showed that on 29th April a secretory endometrium was present whereas on 20th May and 8th June an early proliferative endometrium was present. It can therefore be concluded that an ovulatory cycle was followed by 2 anovulatory cycles.

Figure 7 shows the oestrogen excretion during this time. The first cycle, 7th to 29th April, showed the characteristic oestrogen pattern of an ovulatory cycle except that the ovulatory peak occurred immediately after cessation of bleeding. During the 2 anovulatory cycles the oestrogen levels remained within the range 13 μg. to 30 μg. total oestrogens per 24 hours urine. The raised oestriol values found on 11th and 12th May are not associated with corresponding rises in the oestrone and oestradiol values and therefore do not represent an ovulation peak. They are probably due to some chance interference in the assay, as described by Brown, Bulbrook and Greenwood (1957b) and should be disregarded.

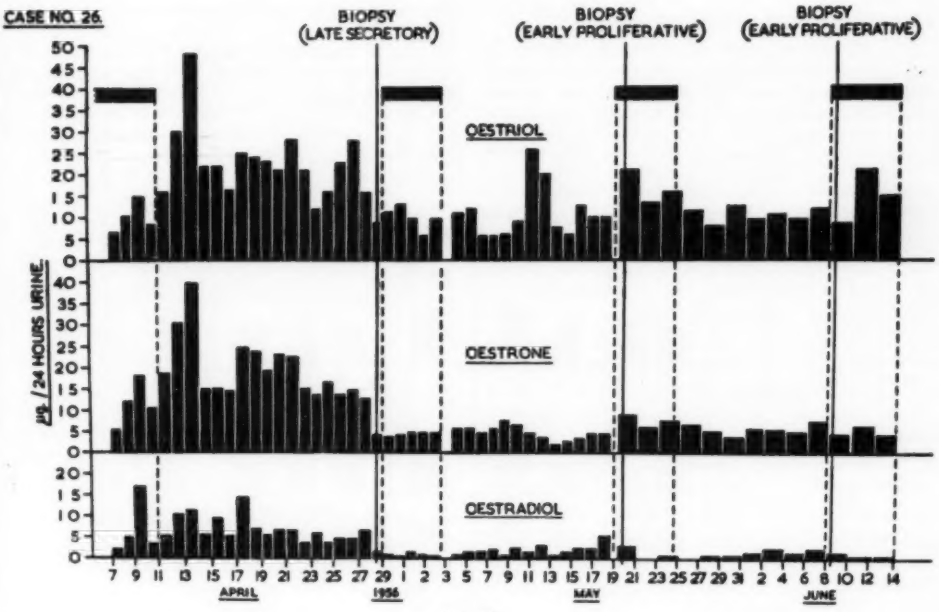

FIG. 7

Case No. 26. Anovulatory menstruation.

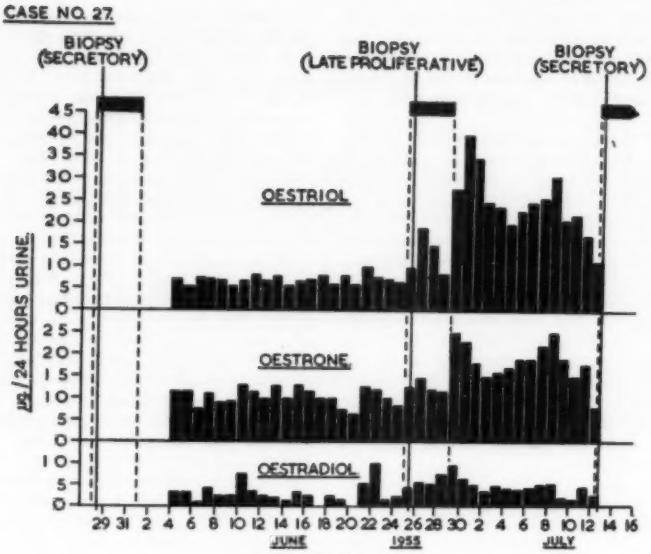

FIG. 8
Case No. 27. Anovulatory menstruation.

Case No. 27 (Fig. 8). Aged 26 years. Para 0+0. This patient was attending the sterility clinic and her menstrual history was one of normal and regular loss. An endometrial biopsy taken on the first day of menstruation commencing 28th May, 1955 showed a normal secretory endometrium. A biopsy taken on the first day of bleeding commencing 25th June showed a late proliferative endometrium while that taken on 13th July, when the next menstrual period began, was in the full secretory phase. It can therefore be concluded that this is an example of an isolated anovulatory cycle occurring between 2 ovulatory cycles.

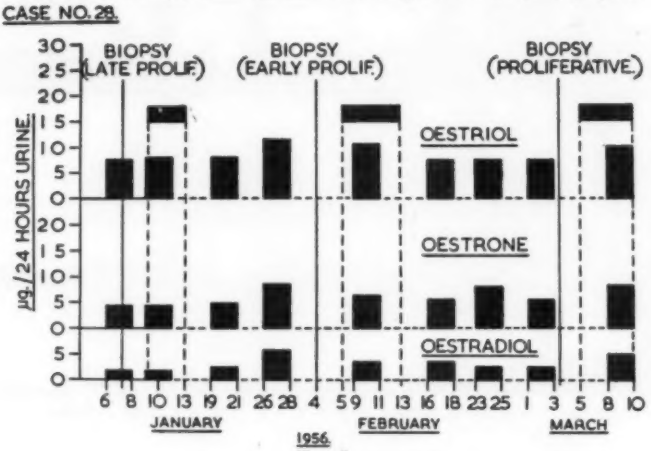

FIG. 9
Case No. 28. Anovulatory menstruation.

Figure 8 shows the urinary oestrogen excretion measured during the latter 2 cycles. During the 3 weeks preceding the onset of anovulatory bleeding on 25th June the daily total oestrogen excretion remained practically constant at approximately 20 μg. The following cycle showed the characteristic oestrogen pattern of an ovulatory menstrual cycle except that the follicular phase was shortened.

Case No. 28 (Fig. 9). Aged 24 years. Para 0+0. From the menarche at 16 years, this patient's menstrual history was one of irregularity, the episodes of bleeding occurring every 4 weeks to 10 months and the flow lasting 7 to 10 days. Urine collections were made sporadically between 6th January and 10th March, 1956. Regular periods of bleeding occurred from 9th to 13th January, from 5th to 13th February, and from 5th to 10th March. Endometrial biopsies performed before each of these episodes of bleeding revealed a late, an early, and a late proliferative endometrium respectively. It can therefore be concluded that these were anovulatory menstrual cycles.

Figure 9 shows the levels of oestrogen excretion found during this time. These were maintained constantly within the range 15 μg. to 26 μg. total oestrogens per day.

Case No. 29 (Fig. 10). Aged 24 years. Para 0+0. Since the menarche at 13 years the history was of alternating periods of amenorrhoea lasting 3 to 6 months and extremely profuse bleeding lasting 7 to 10 days. This patient had, in fact, twice received blood transfusions at the age of 20 and 23 years because of exsanguination. However, her recent menstrual periods had been more regular, commencing on 25th June, 16th August and 14th September, 1956. A curettage performed on 15th September showed a late proliferative endometrium with many cystic glands. It can therefore be concluded that this was an anovulatory menstrual cycle.

Oestrogen determinations were performed from 3rd to 21st September, 1956 (Fig. 10). The total oestrogen excretion was maintained during this time between 12 μg. to 23 μg. per day.

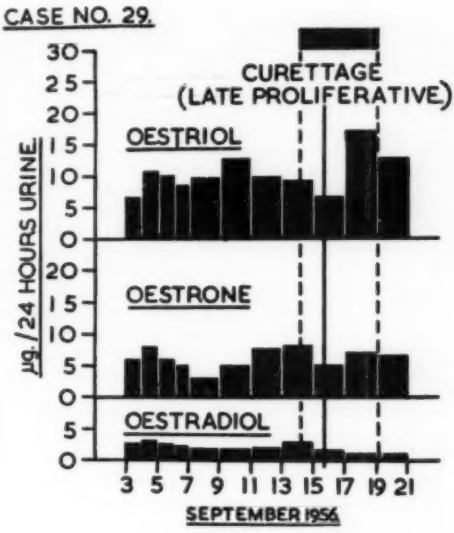

FIG. 10

Case No. 29. Anovulatory menstruation.

The characteristic feature of the urinary oestrogen excretion pattern during the anovulatory cycles studied is the constancy of the amounts excreted at all times of the cycle. This contrasts with the rhythmical rise and fall in oestrogen levels observed during ovulatory cycles. The oestrogen levels found during anovulatory cycles were maintained in the range 13 μg. to 30 μg. total oestrogens per 24-hours urine. The oestrogen levels found during the 11 anovulatory menstrual cycles occurring in 6 patients were: actual range (for 116 observations); oestriol 5·0 μg. to 21 μg. (mean 9·4 μg. ± 2·7 μg.*); oestrone 3·0 μg. to 13·0 μg. (mean 6·4 μg. ± 2·3 μg.*); oestradiol nil to 10·2 μg. (mean 2·4 μg. ± 1·7 μg.*); total 9·3 μg. to 33·1 μg. (mean 18·2 μg. ± 4·1 μg.*). These figures are considerably greater than those found in post-menopausal women who do not show endometrial stimulation. It seems that these amounts of urinary oestrogens reflect threshold levels of oestrogens in the body which are sufficient to stimulate growth of the endometrium. As the endometrium builds up under this steady stimulation, it apparently becomes unstable and breaks down from time to time resulting in anovulatory bleeding from a proliferative phase endometrium. Unlike normal menstruation, this bleeding occurs without withdrawal of the oestrogenic (and progestogenic) stimulus. These conditions appear analogous to those produced experimentally by Zuckerman and others who found that uterine bleeding will occur periodically in oöphorectomized monkeys and women maintained on a constant threshold dose of oestrogen

* Standard deviation.

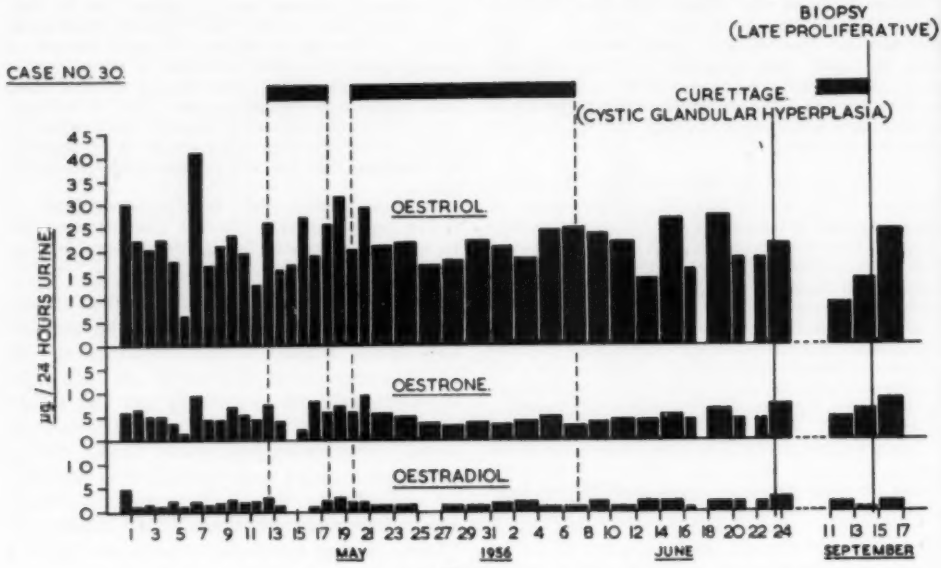

FIG. 11

Case No. 30. Cystic glandular hyperplasia.

(Zuckerman, 1949). It is interesting to note that in all the cases where an ovulatory cycle followed a period of anovulatory bleeding, the ovulation peak occurred immediately after the cessation of bleeding.

Group II. Cystic Glandular Hyperplasia

As in the previous group, it has been difficult to obtain complete oestrogen studies on cases of cystic glandular hyperplasia during the phase of endometrial build-up. Complete information has been obtained on only 2 of the many cases investigated. Fortunately, these 2 cases, Nos. 30 and 31, show two clearly different patterns of oestrogen excretion which can be associated with cystic glandular hyperplasia. The remaining less completely studied cases, however, provide supporting evidence for the general applicability of the findings.

Case No. 30 (Fig. 11). Aged 27 years. Para 0+0. This patient's menstrual history was one of prolonged phases of amenorrhoea and of irregular menstruation at intervals of 30 to 90 days.

Bleeding occurred from 12th until 17th May, 1956. After stopping for 2 or 3 days, a slight loss was experienced until 7th June. Curettage was performed on 23rd June and a well-developed cystic glandular hyperplasia of the endometrium was found. This patient was re-admitted on 10th September, 1956 and stated that she had experienced more or less continuous loss for 9 weeks since 7th July. Bleeding ceased following a few days in bed. A biopsy performed at this time showed an active late proliferative endometrium.

Figure 11 shows the results of oestrogen assays performed during the months of May, June and September. The total oestrogen excretion remained within the range 20 μg. to 40 μg. per 24 hours during the whole study. In this patient, therefore, cystic glandular hyperplasia was associated with daily total urinary oestrogen levels of approximately 30 μg., which were maintained for a considerable period of time. Menstrual bleeding occurred at these levels. This pattern of constant oestrogen excretion is therefore analogous to that of an anovulatory menstrual cycle except that the oestrogen levels were maintained at somewhat higher figures.

Case No. 31 (Fig. 12). Aged 43 years. Para 5+0. This patient stated that her menstrual periods had been heavy and irregular for almost one year and curettings obtained on 17th September, 1956 showed the typical changes of cystic glandular hyperplasia. On 6th December, 1956 a further curettage revealed the same

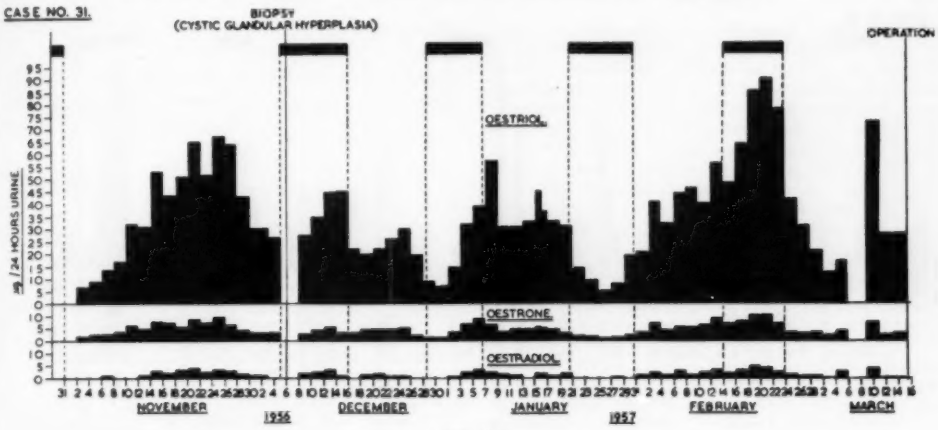

FIG. 12

Case No. 31. Cystic glandular hyperplasia.

changes in the endometrium; this curettage was carried out the day following the onset of bleeding. Further heavy losses occurred on 29th December, 1956, 20th January, 1957 and 14th February, 1957. Hysterectomy was advised and this, without removal of the appendages, was carried out on 15th March. Examination of the endometrium at operation showed an early secretory phase. Urine was collected for oestrogen estimations from 2nd November, 1956 until 15th March, 1957. Figure 12 shows the results obtained. Estimations were generally performed on 48-hours specimens of urine. In contrast with Case No. 30, the urinary oestrogen levels rose and fell in a very definite manner. At the beginning of November, the urinary oestrogen levels were low, being approximately 10 μg. total oestrogens per 24-hours urine. They then increased gradually to reach 80 μg. total oestrogens per 24 hours on 24th and 25th November and then decreased. It will be noted that the levels remained above 35 μg. per day for 20 days, that bleeding occurred as the levels were decreasing, and that the endometrium at the time of bleeding showed cystic glandular hyperplasia. Although this rise was similar in height to the ovulatory peak of an ovulatory cycle, it lasted for a much longer time. It is likely that these high levels, maintained for an abnormally long period of time, were the cause of the cystic glandular hyperplasia. The particular episode of bleeding which followed the rise could have resulted from the withdrawal of the oestrogenic stimulus. During December, the oestrogen levels rose to a peak resembling an ovulation peak, when bleeding ceased; they fell and rose again to a second maximum resembling the luteal maximum of an ovulatory menstrual cycle. Bleeding recommenced 14 days after the first peak as the levels were falling. The oestrogen excretion pattern was therefore consistent with ovulation having taken place during this cycle. Although no other tests were performed to prove this, the finding of a secretory endometrium at operation indicated that the occurrence of ovulation during December was a likely possibility. However, even this cycle cannot be classified as "normal" since the bleeding phase lasted for 11 days. A similar sequence of events during January suggested that ovulation also occurred during that month. During February, the oestrogen excretion pattern resembled that found during November, the rise being even higher and more prolonged. The levels remained above 45 μg. per day for 24 days and, at their highest, reached 100 μg. No endometrial biopsy was taken at this time but there is every reason to believe that the picture would have been the same as that following the November peak, namely cystic glandular hyperplasia. An important feature of the February events was that bleeding commenced while the oestrogen levels were high and were still rising. Levels had been maintained above 40 μg. per day for 12 days before this. It is possible that the endometrium had proliferated to such an extent during this time that, in the absence of the progestational stimulus of a corpus luteum, it had become unstable and had broken down to cause the bleeding observed. This, in effect, resembles the sequence found in Case No. 30 where bleeding was associated with the maintenance over a period of time of elevated oestrogen levels. Another surprising feature of the February events was that the bleeding stopped as the oestrogen levels were falling. There is at present no explanation for this. The elevated levels noted on the 9th to 11th March were probably part of an ovulation peak since an early secretory endometrium was found 4 days later at operation.

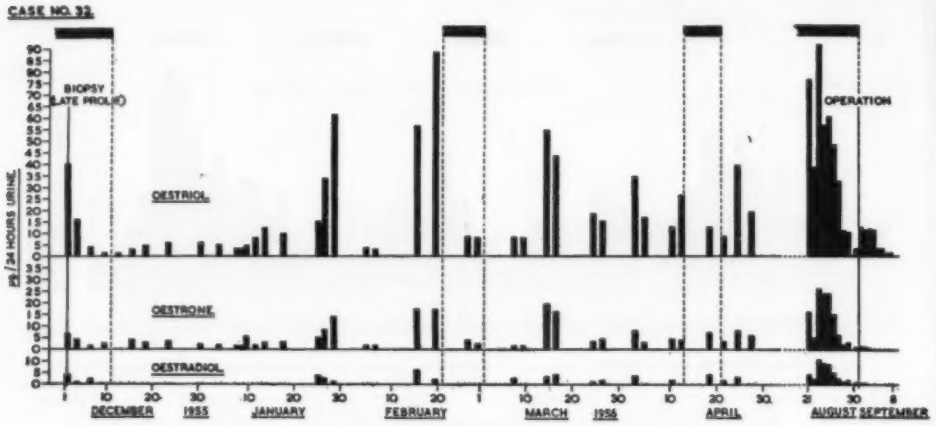

FIG. 13

Case No. 32. Cystic glandular hyperplasia.

The results obtained in Cases Nos. 30 and 31 show that:

(1) Cystic glandular hyperplasia of the endometrium is found in association with total urinary oestrogen levels which have been maintained for some time in the region of 30 μg. per day or more.

(2) The oestrogen levels may remain constant as in anovulatory cycles, or rise and fall as in ovulatory menstrual cycles. However, the rise and fall occur as a broad maximum which does not resemble the sharp ovulation peak of a menstrual cycle. Peak levels may be higher than those found during normal menstrual cycles.

(3) Bleeding from this type of endometrium may occur while the urinary oestrogen levels are constant, while they are rising, or while they are falling.

The subsequent cases illustrate the generality of these findings.

Case No. 32 (Fig. 13). Aged 37 years. Para 0+0. This patient gave a history of irregular and excessive menstruation for 3 years. A curettage performed on 22nd March, 1955 showed cystic glandular hyperplasia. Following this operation, menstrual function improved but bleeding which began in early October continued until December when oestrogen assays were commenced. An endometrial biopsy taken on 1st December, 1955 while the patient was still bleeding, showed a late proliferative endometrium. Urine collections were made sporadically from 1st December, 1955 until the end of April, 1956 and then again in August while the patient was in hospital awaiting hysterectomy. While the observations are by no means complete, they show the same pattern as the results obtained from Case No. 31. The total oestrogen levels fluctuated from 5 μg. per day to more than 100 μg. per day. On 19th February she was excreting over 100 μg. per day when bleeding ensued and lasted for 10 days. Oestrogen levels determined during the bleeding phase were approximately 15 μg. per day. The total oestrogen excretion on the days preceding the onset of bleeding on 13th April was 20 μg. to 30 μg. per day. This bleeding lasted until 21st April. Thereafter the patient had amenorrhoea for 10 weeks. Bleeding commenced again on 25th June and lasted for 9 weeks until hysterectomy was performed on 31st August. Oestrogen determinations were made for the 11 days preceding operation. During this time the levels were above 100 μg. per day and fell to less than 10 μg. per day without affecting the course of bleeding. Histological examination of the hysterectomy specimen showed the presence of cystic glandular hyperplasia.

This is another case in which cystic glandular hyperplasia was associated with high and fluctuating levels of urinary oestrogens. The ovaries were not removed at operation. It is interesting to note that if assays had been performed at the time of hysterectomy only, the findings would have been misleading in that they would have shown low post-menopausal

oestrogen levels associated with cystic glandular hyperplasia. This illustrates the futility of limited observations in these cases and probably accounts for such findings in some of the other patients in this series.

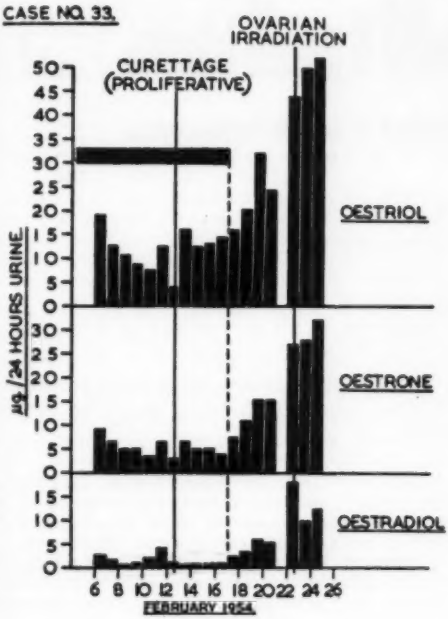

FIG. 14

Case No. 33. Cystic glandular hyperplasia.

Case No. 33 (Fig. 14). Aged 45 years. Para 0+0. This patient's menstrual history was one of increasing irregularity and prolonged loss. In July, 1953 she underwent a curettage and the endometrium showed cystic glandular hyperplasia. Through the rest of the year menstruation was less irregular but still excessive in duration. In December bleeding lasted for 16 days. Bleeding re-commenced on 20th January, 1954 and continued until 17th February. She was admitted to hospital on 6th February and urine collections were commenced. A curettage was carried out on 12th February and the histological picture obtained was that of a late proliferative endometrium with many dilated glands, that is, something short of a full cystic glandular hyperplasia. During 22nd to 24th February an artificial menopause was induced by means of ovarian irradiation by X-ray, and on 25th February the patient was discharged. Further specimens of urine could not be obtained for assay after this date. The results of oestrogen assays are shown in Figure 14. At first the daily total oestrogen excretion was of the order of 15 μg. to 25 μg. At that time curettage showed a late proliferative endometrium. The oestrogen excretion then began to rise and, on the days when the ovaries were being irradiated, reached the high levels of 88 μg. to 95 μg. per day. In the absence of further investigations it is difficult to interpret these findings. It is possible that the oestrogen levels were rising to an ovulation peak or to the broad maximum frequently associated with cystic glandular hyperplasia. Yet again, the high levels might have been due to a temporary stimulation of the ovaries by irradiation.

Case No. 34. Aged 50 years. Para 3+0. This patient's menstrual history was one of excessively long periods of bleeding which occurred every 2 to 3 months. For example a menstrual period lasted from 19th February to 9th March, 1954. In view of poor general health and low haemoglobin (60 per cent), hysterectomy was advised and this, with bilateral salpingo-oöphorectomy, was performed on 26th March. The endometrium at this time showed cystic glandular hyperplasia. *Oestrogen Assays:* 6×24 hours urinary collections were made in the immediate pre-operative period. Range: oestriol nil to 2·2 μg. (mean 1·2 μg.); oestrone 0·6 μg. to 2·2 μg. (mean 1·5 μg.); oestradiol nil to 1·2 μg. (mean 0·4 μg.); total 1·2 μg. to 4·8 μg. (mean 3·1 μg.). Post-operative period: 1×24 hours urinary collection was submitted for assay. Results: oestriol 2·6 μg., oestrone 1·2 μg., oestradiol 0·8 μg., total 4·6 μg.

In this case post-menopausal oestrogen levels were associated with cystic glandular hyperplasia. The probable explanation for this is discussed in Case No. 32.

Case No. 35. Aged 54 years. Para 3+0. This patient had a history of irregular menstrual periods for 6 years. The last episode of bleeding was associated with heavy loss and lasted from 3rd until 19th April, 1954. The patient was admitted to hospital on 19th April and a hysterectomy with bilateral salpingo-oöphorectomy was carried out on the 23rd. The endometrium showed cystic glandular hyperplasia. *Oestrogen Assays:* 1×24 hours pre-operative urinary assay was carried out. Results: oestriol 0·5 μg., oestrone 1·2 μg., oestradiol 0·2 μg., total 1·9 μg. One×24 hours post-operative urinary collection was made. Results: oestriol 0·5 μg., oestrone nil; oestradiol nil; total 0·5 μg.

The probable explanation for the finding of cystic glandular hyperplasia in the presence of these low oestrogen values is discussed in Case No. 32.

Case No. 36 (Fig. 15). Aged 44 years. Para 1+0. This patient gave a history of regular menstruation until recently when, following a phase of 8-weeks amenorrhoea, bleeding commenced on 1st December, 1954 and

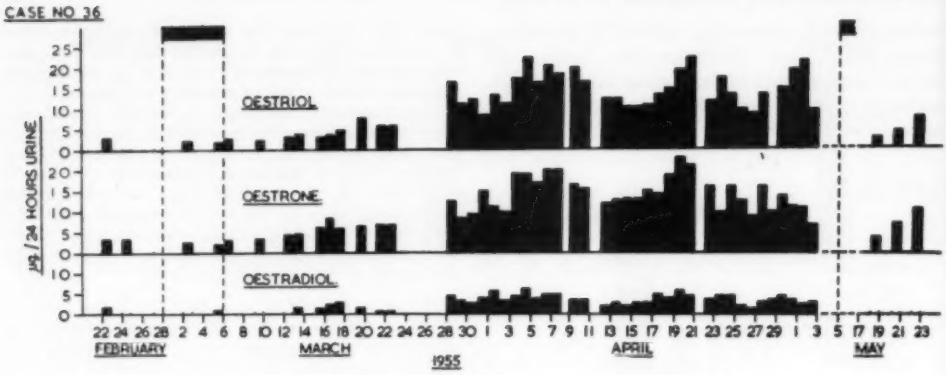

FIG. 15

Case No. 36. Cystic glandular hyperplasia.

lasted 6 weeks. Curettage was performed on 20th January, 1955 and cystic glandular hyperplasia was found. Oestrogen assays were carried out during the months of February, March, April and May. Following a scanty loss from the 28th February until 6th March, there ensued a phase of amenorrhoea which lasted for almost 9 weeks until 5th May. Figure 15 shows the oestrogen excretion during this time. During most of March the total oestrogen excretion remained below 15 μg. daily. By 28th March, the total excretion levels had increased to 30 μg. to 40 μg. daily. They were maintained with minor fluctuations in this range for about 5 weeks. Bleeding commenced on 5th May and lasted only for a few days. No histological examination of the endometrium was performed at this time. A further period of amenorrhoea in May and June was followed by a bleeding from 15th to 21st July and thereafter the menstrual function returned to normal.

In this case, with the presumptive diagnosis of cystic glandular hyperplasia based on previous histological findings, the total urinary oestrogen levels were maintained at the comparatively high figure of 30 μg. to 45 μg. per day for 5 weeks before the onset of bleeding.

Case No. 37. Aged 49 years. Para 3+0. This patient's menstrual history was one of irregular and relatively short periods of bleeding. Bleeding commenced on 26th January, 1956 and continued until admission to hospital at the beginning of March. Curettage on 5th March revealed a very active cystic glandular hyperplasia. *Oestrogen Assays:* 2×24 hours immediately pre-operative urinary collections were made. Range: oestriol 17·4 μg., 22·2 μg.; oestrone 7·8 μg., 7·8 μg.; oestradiol 2·2 μg., 1·7 μg.; total 27·4 μg., 31·7 μg. Two×24 hours post-operative urinary collections were also obtained. Range: oestriol 50·4 μg., 19·8 μg.; oestrone 10·5 μg., 5·4 μg.; oestradiol nil, 0·6 μg.; total 60·9 μg., 25·8 μg.

This case is an example of elevated oestrogen levels associated with cystic glandular hyperplasia.

Case No. 38 (Fig. 16). Aged 36 years. Para 2+0. This patient's menstrual history, over a period of 6 years, was characterized by great irregularity and excessive loss. A curettage carried out on 16th November, 1951 revealed cystic glandular hyperplasia of the endometrium. A further curettage performed on 7th December 1956 showed a persistence of this type of endometrium. Following this curettage she had a period of amenorrhoea until March, 1957 when bleeding recommenced.

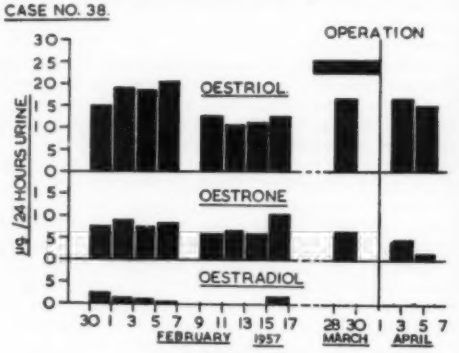

FIG. 16

Case No. 38. Cystic glandular hyperplasia.

Hysterectomy with right salpingo-oöphorectomy was performed on 1st April. The endometrium at this time showed typical cystic glandular hyperplasia.

Urinary collections were made sporadically during February, March and April, 1957. Figure 16 shows the results obtained. For a period of almost 3 weeks in February the total oestrogen excretion lay between 17 μg. and 30 μg. daily. One estimation performed during the bleeding phase in March showed the same values. It can therefore be concluded that levels of 17 μg. to 30 μg. total oestrogen per day had probably been maintained for a period of at least 8 weeks.

The results here resemble those found in Case No. 30.

Case No. 39. Aged 50 years. Para 4+0. This patient's menstrual history was one of relatively infrequent but profuse and prolonged periods. She was curetted on 28th December, 1956 and cystic glandular hyperplasia was found. During January, 1957 she had 2 comparatively short menstrual periods but one occurring on 19th February lasted for 6 days and was very profuse. Hysterectomy with bilateral salpingo-oöphorectomy was performed on 15th March. At this time the endometrium showed an active cystic glandular hyperplasia. Oestrogen assays were performed on 5×48 hours urinary specimens collected immediately before hysterectomy. Range: oestriol 6·2 μg. to 40 μg. (mean 22·7 μg.); oestrone 2·0 μg. to 12·0 μg. (mean 6·6 μg.); oestradiol nil to 2·9 μg. (mean 1·3 μg.); total 8·2 μg. to 55 μg. (mean 30·6 μg.).

This case is an example of elevated oestrogen levels associated with cystic glandular hyperplasia.

Case No. 40 (Fig. 17). Aged 44 years. Para 3+1. This patient's menstrual history had previously been quite normal. However, because of a prolonged bout of bleeding, she was curetted on 13th December, 1956 and cystic glandular hyperplasia was found. Little benefit followed this operation for, although she had a short menstrual period from 30th January to 3rd February, 1957 uterine bleeding recommenced on 12th February and continued until hysterectomy with bilateral salpingo-oöphorectomy was performed on 8th March. At this time the endometrium again showed cystic glandular hyperplasia. Figure 17 shows the results of oestrogen assays performed on urine collected before, during and after operation. On the 4 pre-operative days the total amounts excreted were between 40 μg. and 60 μg. per day. Following hysterectomy and removal of the ovaries, the urinary oestrogen levels decreased rapidly and reached post-menopausal levels in 5 days.

This case shows high oestrogen levels associated with cystic glandular hyperplasia. Removal

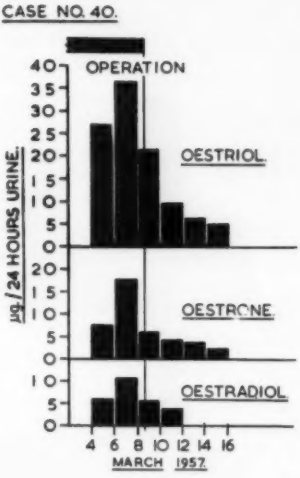

FIG. 17

Case No. 40. Cystic glandular hyperplasia.

of the ovaries was followed by a prompt fall in urinary oestrogens to post-menopausal levels.

Case No. 41. Aged 16 years, Para 0+0. Until January, 1957 the menstrual cycle had been regular since the menarche at 14 years. A menstrual period commencing on 4th January lasted until the 15th. On 22nd February bleeding recommenced and continued until curettage was performed on 18th March, 1957. At this time the endometrium showed cystic glandular hyperplasia. Oestrogen assays were performed on 2×48 hours urinary collections made just after the curettage. Range: oestriol 5·8 μg., 7·8 μg.; oestrone 4·0 μg., 3·7 μg.; oestradiol 1·1 μg., 1·7 μg.; total 10·9 μg., 13·2 μg. per 24 hours.

These values are compatible with weakly stimulating levels of oestrogens but are unlikely to have produced cystic glandular hyperplasia. It is more probable that this case is similar to Case No. 32.

Case No. 42 (Fig. 18). Aged 40 years. Para 5+1. This patient had a history of irregular and excessive menstruation for over a year. On 28th February, 1957, when heavy bleeding had continued for 15 days, curettage was performed and the endometrium showed cystic glandular hyperplasia. Bleeding, which was not excessive, began again on 6th April and lasted for 6 days. Another curettage performed on 17th May also showed cystic

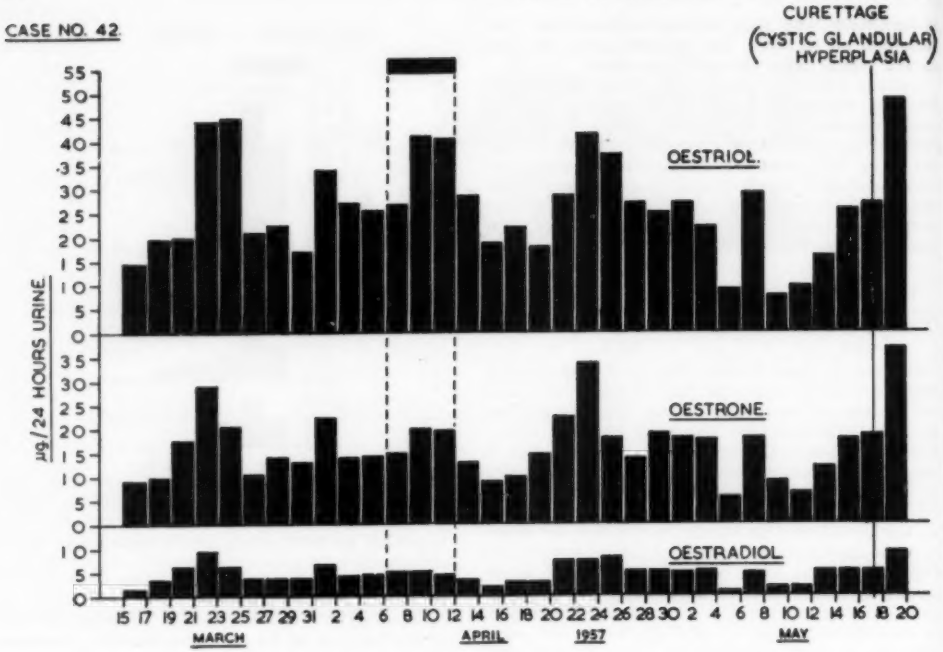

FIG. 18

Case No. 42. Cystic glandular hyperplasia.

glandular hyperplasia of the endometrium. Bleeding recommenced on 30th June, 1957 and continued until hysterectomy with bilateral salpingo-oöphorectomy was performed on 28th July. Examination of the extirpated uterus and appendages revealed an ovary containing a corpus luteum about 4 days old and cystic endometrium showing early secretory changes. Urinary collections were made from 15th March until 20th May. Figure 18 shows the results of oestrogen assays performed during this time. The levels fluctuated between 16 µg. and 95 µg. total oestrogens per 24 hours.

This is another example of the association of cystic glandular hyperplasia with high and fluctuating levels of urinary oestrogens. The peaks which occurred on 21st to 23rd March and 22nd to 24th April resembled the ovulation peak of an ovulatory menstrual cycle but the subsequent rises and falls characteristic of the luteal phase did not occur. The findings at operation of a recent corpus luteum and a cystic endometrium showing early secretory changes lend support to the belief that ovulation was occurring at intervals in this patient. However, in the absence of further tests of corpus luteum function such as pregnanediol determinations or more frequent endometrial biopsies, it is difficult to draw further conclusions from this case.

Case No. 43 (Fig. 19). Aged 46 years. Para 5+0. This patient had developed irregular and excessive menstrual bleeding over a period of some 10 months. Curettage on 27th September, 1956 revealed cystic glandular hyperplasia. The subsequent 2 menstrual periods were not excessive but bleeding which commenced on 15th February, 1957 lasted until 31st March. Further slight bleeding was recorded on 10th and 11th April. Urinary collections were made from 12th to 30th April. An artificial menopause was induced by the insertion of intra-uterine radium on 22nd April.

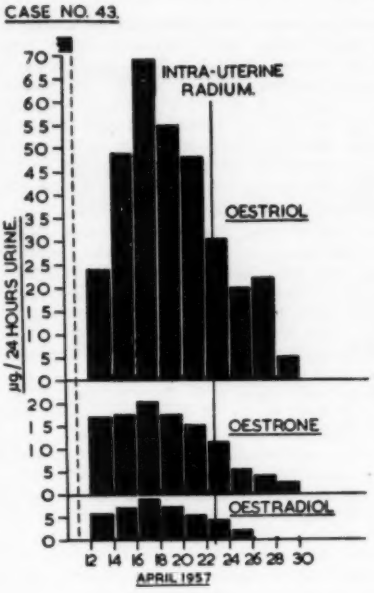

FIG. 19

Case No. 43. Cystic glandular hyperplasia.

Figure 19 shows the results of the oestrogen assays. The oestrogen levels rose from a total of 50 μg. per day on 12th April to a peak of 100 μg. per day on the 16th and then decreased. After the insertion of radium, the levels decreased rapidly and reached post-menopausal levels within 7 days.

This case shows high fluctuating levels of oestrogens in a patient in whom the presumptive diagnosis of cystic glandular hyperplasia was based upon previous histological findings.

Case No. 44. Aged 49 years. Para 8+0. This patient complained of menstrual irregularity and excessive loss over many months. She experienced 12-weeks bleeding over the months October, November and December, 1953 and January, 1954. Hysterectomy with bilateral salpingo-oöphorectomy was performed on 26th January, 1954. At this time, 16 days after the cessation of bleeding, a late proliferative endometrium with several cystic glands, but not the full picture of cystic glandular hyperplasia, was found.

Oestrogen assays were performed on 2×24 hours urinary specimens collected on the 2 days prior to operation. Range: oestriol 62 μg., 58 μg.; oestrone 35 μg., 22 μg.; oestradiol 9·0 μg., 11·0 μg.; total 106 μg., 91 μg., per 24 hours. Two weeks after hysterectomy and bilateral oöphorectomy the oestrogen levels were: oestriol 1·1 μg., 0·8 μg.; oestrone 1·0 μg., 1·1 μg.; oestradiol nil, nil; total 2·1 μg., 1·9 μg.

This case shows high levels of urinary oestrogens associated with an early picture of cystic glandular hyperplasia. Urinary oestrogen excretion decreased to post-menopausal levels after bilateral oöphorectomy.

Group III. Other Forms of Dysfunctional Uterine Bleeding

The clinician has found it very difficult to classify and understand the comparatively large group of patients suffering from dysfunctional uterine bleeding who do not fall into the clearly defined groups of anovulatory menstrual cycles or of cystic glandular hyperplasia. Carefully timed endometrial biopsies are not necessarily of absolute diagnostic value as, all too frequently, they provide only a broad basis for the division of cases into those in whom there is evidence of a progestogenic effect and those, the large majority, in whom it is clear that no such effect exists. Suitable cases for study are peculiarly difficult to collect and little worthwhile information can be obtained without study over many weeks. The subsequent case histories are illustrative of this type of dysfunctional uterine haemorrhage.

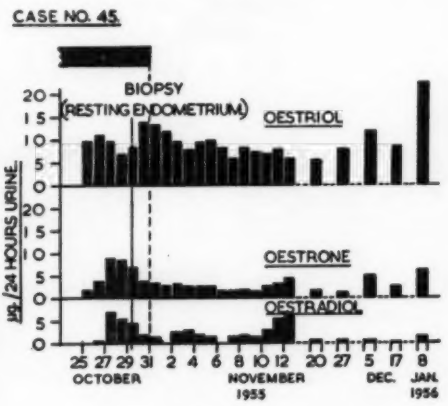

FIG. 20

Case No. 45. Dysfunctional uterine haemorrhage.

Case No. 45 (Fig. 20). Aged 43 years. Para 0+0. For most of her menstrual life this patient experienced normal and regular periods. For the preceding 5 years, however, menstruation had been irregular both in time and duration. Bleeding which began on 3rd October, 1955 was still continuing on 29th October when an endometrial biopsy was performed. An almost atrophic "resting" endometrium was found at this time.

Oestrogen assays were performed from 25th October until 13th November and then sporadically until 8th January, 1956. At the time of biopsy, when an atrophic endometrium was found, the total oestrogen levels had been maintained in the range 13 μg. to 25 μg. per day since the start of assays 4 days earlier. Furthermore, they remained practically within this range for the remainder of the study. These levels are usually associated with proliferative changes in the endometrium. The finding of an atrophic endometrium might have been due to complete shedding of the endometrium during the preceding 4 weeks of bleeding. Another and more likely possibility is that the biopsy specimen, limited to one strip of endometrium, was not necessarily representative of the endometrium as a whole.

Case No. 46. Aged 47 years. Para 0+0. In this case menstruation had been regular until 19th March, 1956 when bleeding commenced and continued until the end of the month. The next menstrual period, also a profuse one, lasted from 26th April until 7th May. Uterine fibroids were diagnosed and hysterectomy with bilateral salpingo-oöphorectomy was performed on 19th May. Examination of the specimen showed that the fibroids present did not anatomically affect the endometrial cavity. The endometrium itself was in a late proliferative phase, that is, 24 days after the onset of the previous menstrual period on 26th April.

Oestrogen assays were performed on urinary collections made during the 3 days immediately preceding operation. Range: oestriol 6·9 μg. to 13·8 μg. (mean 11·1 μg.); oestrone 10·2 μg. to 20·4 μg. (mean 16·2 μg.); oestradiol 1·4 μg. to 6·2 μg. (mean 3·8 μg.); total 18·5 μg. to 40·4 μg. (mean 31·1 μg.). These figures represent oestrogen levels which are usually associated with stimulation of the endometrium and, in fact, no recent corpus luteum was found in the ovaries removed at operation.

Case No. 47 (Fig. 21). Aged 20 years. Para 0+0. From the menarche at 15 years, this patient complained that the interval between menstruation varied from 2 to 12 weeks. The duration of the flow was usually only one week, but bleeding which commenced on 21st March, 1956 lasted for 10 weeks until 26th May. Curettage performed on 1st June, 1956 showed a late proliferative endometrium.

Urinary oestrogens were measured from 22nd May until 3rd July. Figure 21 shows the results obtained. From 22nd May until 17th June the total amount of oestrogens excreted daily was between 10 μg. and 18 μg. The amounts then increased to a peak of 55 μg. on 21st June, fell and then rose again. The peak resembled the ovulation peak of an ovulatory menstrual cycle. Bleeding began 16 days after the peak, but a biopsy was not obtained to confirm that ovulation had occurred. However, the oestrogen excretion pattern during the month of June strongly suggests that ovulation did occur.

This case is an example of the occurrence of spontaneous ovulation following a grossly prolonged proliferative phase.

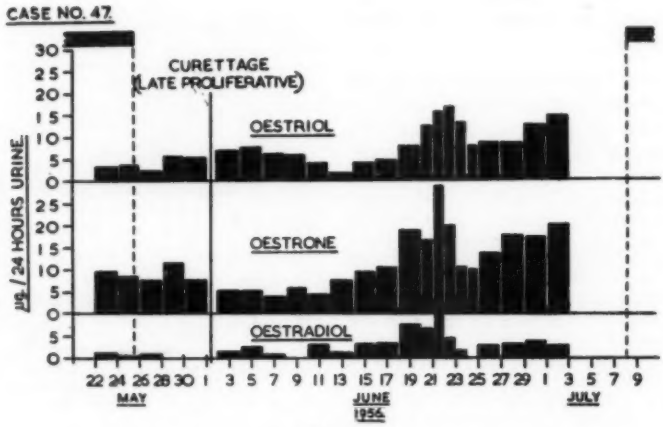

FIG. 21

Case No. 47. Dysfunctional uterine haemorrhage.

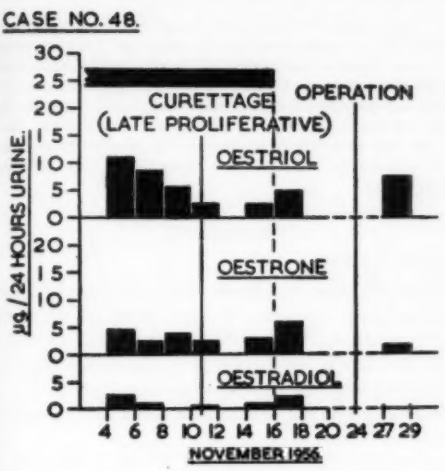

FIG. 22

Case No. 48. Dysfunctional uterine haemorrhage.

Case No. 48 (Fig. 22). Aged 46 years. Para 1+1. For 2 years this patient had experienced irregular uterine bleeding. From July until the beginning of October, 1956 there was amenorrhoea. Bleeding commenced in October and continued until 16th November. Curettage was performed on 11th November, during the bleeding phase, and a late proliferative endometrium was found. As the uterus contained fibroids, hysterectomy with bilateral salpingo-oöphorectomy was carried out on 24th November.

Figure 22 shows the results of oestrogen assays performed from 4th November, after 4-weeks bleeding, until 18th November. The total oestrogen excretion was approximately 17 μg. per day on 4th to 6th November and then decreased to approximately 5 μg. per day. Under these conditions the endometrium obtained by curettage was quite thick and showed a late proliferative phase. A similar endometrial picture was found at hysterectomy.

Case No. 49. Aged 39 years. Para 2+0. In this case menstruation had been regular until 1955 but during the past year had become irregular with heavy loss. Bleeding, which commenced on 5th November, 1956 continued for 23 days until 28th November. On 10th December curettage was performed and a very early secretory endometrium was found. The next episode of bleeding occurred on 16th December and thereafter her menstrual function returned to normal. Oestrogen assays were performed on 2×48 hours urinary specimens collected from 9th to 12th December. The consecutive results were: oestriol 12·6 μg., 19·2 μg.; oestrone 5·2 μg., 6·0 μg.; oestradiol 1·5 μg., 2·0 μg.; total 19·3 μg., 27·2 μg.

Whilst these isolated results have little meaning in themselves, they are compatible with luteal phase oestrogen levels. This is another patient in whom spontaneous ovulation occurred following a prolonged episode of bleeding.

Case No. 50 (Fig. 23). Aged 41 years. Para 6+2. In this case menstrual function had been normal until 9th January, 1957 when she commenced a period of bleeding which lasted until 25th January. Because of this she was curetted on 4th February and an early prolifera-

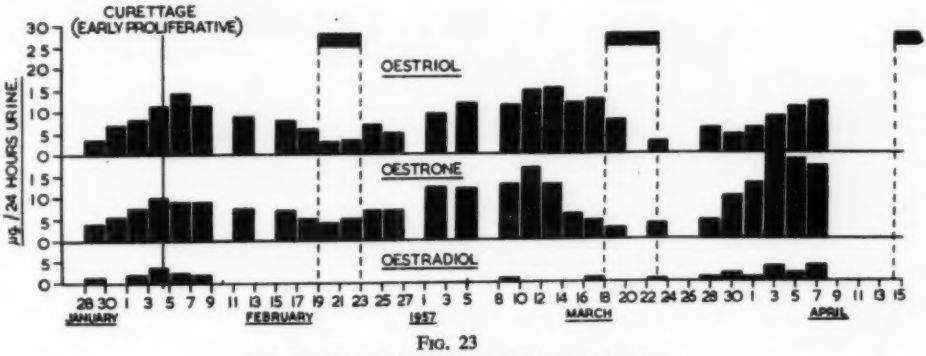

FIG. 23

Case No. 50. Dysfunctional uterine haemorrhage.

tive endometrium was found. Thereafter she had regular bleeding phases which commenced on 19th February, 18th March and 15th April.

Urinary oestrogen determinations were made sporadically on 48-hours specimens of urine during January, February, March and April, 1957. Figure 23 shows the results obtained. Regular rises and falls between approximately 7 μg. to 35 μg. total oestrogens per day occurred between each bleeding phase. In the absence of endometrial biopsies taken at the time of bleeding or of more frequent oestrogen assays, it is impossible to state whether these were ovulatory or anovulatory cycles.

Case No. 51. Aged 20 years. Para 0+0. This patient, who showed clinical evidence of genital hypoplasia, had experienced relatively infrequent menstruation for 2 years. After a period of 6-months amenorrhoea, bleeding commenced on 28th December, 1956 and lasted almost continuously until 16th March, 1957 when she was curetted. No endometrium was obtained. This patient subsequently had apparently normal menstruation in April, May and June, 1957. Urinary oestrogen assays were performed on 4×48 hours urinary specimens collected between 9th and 15th, and 19th and 21st March, 1957. Range: oestriol 8·5 μg. to 17·5 μg. (mean 12·0 μg.); oestrone 9·5 μg. to 13·3 μg. (mean 11·8 μg.); oestradiol 3·3 μg. to 6·5 μg. (mean 4·9 μg.); total 24·6 μg. to 33·4 μg. (mean 28·7 μg.). It is difficult to explain the lack of curettings in the presence of these levels of oestrogens which are usually associated with a stimulated endometrium. The possibilities are that the endometrium had been completely shed during the preceding episode of bleeding or, alternatively, that there was no response to these levels of oestrogens from an insensitive endometrium associated with uterine hypoplasia.

Section III

Amenorrhoea

Twenty-four patients are included in this group and, of these, 4 were cases of primary amenorrhoea, 3 being due to congenital absence of the uterus and vagina. The remaining 20 patients were cases of secondary amenorrhoea of a duration varying from 7 weeks to 13 years.

Case No. 52 (Fig. 24). Aged 20 years. This was a case of congenital absence of the uterus and vagina but there was normal development of secondary sex characteristics. The patient was admitted to hospital for construction of an artificial vagina, and during

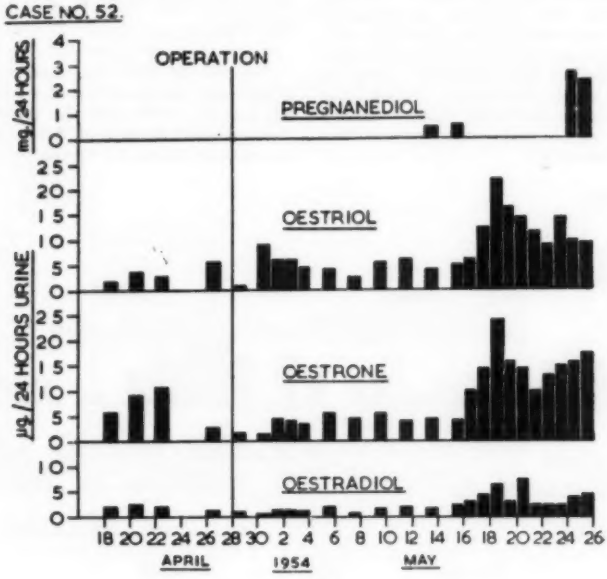

Fig. 24

Case No. 52. Amenorrhoea. Congenital absence of uterus and vagina.

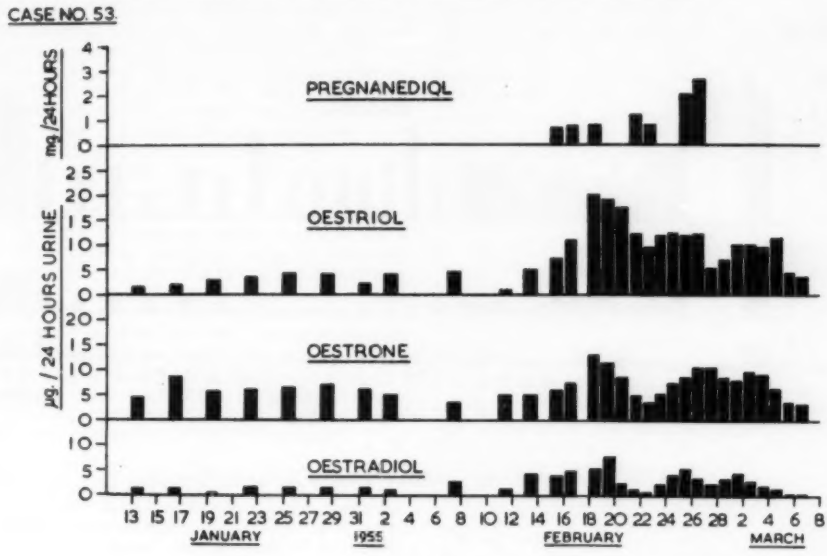

FIG. 25

Case No. 53. Amenorrhoea. Congenital absence of uterus and vagina.

her stay in hospital between 18th April and 25th May, 1954, 25 assays of urinary oestrogens were made on 24-hours collections of urine. The results are illustrated in Figure 24. It will be noted that from admission, for a period of 29 days, the oestrogen levels were consistent with the proliferative phase of the menstrual cycle. This phase was followed by a typical ovulation peak on 18th May, 1954 and for the remainder of the period of hospitalization, until 26th May, 1954, the levels were those of the luteal phase of a normal menstrual cycle. Confirmation of ovulation and luteal activity was provided by the increased excretion of urinary pregnanediol.

Case No. 53 (Fig. 25). Aged 21 years. This was a patient with congenital absence of uterus and vagina. There was normal development of secondary sex characteristics and she was admitted to hospital for the operative construction of an artificial vagina. During her period of hospitalization, from 13th January, 1955 until 7th March, 1955, 30 assays were made on 24-hours urinary collections. From 13th January, 1955 until 13th February, 1955 the levels were those of the proliferative phase of a menstrual cycle. Thereafter the levels rose to an ovulation peak on 18th February, 1955. Subsequently the levels were consistent with a normal luteal phase. Confirmation of ovulation and luteal activity was provided by the rising urinary pregnanediol levels and by laparotomy, carried out on 18th May, 1955 which demonstrated the presence of normal ovaries showing both cystic follicles and corpora lutea.

Case No. 54 (Fig. 26). Aged 33 years. This was a case of congenital absence of the uterus and vagina. There was normal development of the secondary sex characteristics and the patient was admitted to hospital in September, 1955 for the construction of an artificial vagina. Oestrogen assays were carried out during September, October and November and the results are recorded in Figure 26. From a study of the chart it would appear that a peak of secretory activity, perhaps a luteal maximum or an ovulation peak, occurred on 9th September and an ovulation peak occurred on 11th November. There is, therefore, reasonable evidence of cyclical ovarian function in the absence of the target organ, the uterus.

Case No. 55. Aged 33 years. Para 0+0. From the age of 13 years, menstruation was regular until January, 1952 when the last menstrual period occurred. After a period of amenorrhoea lasting for one year, at the age of 31 years, laparotomy was performed on 8th February, 1953 when a left combined granulosal and thecal celled ovarian tumour was removed. Following operation, amenorrhoea continued and a diagnostic curettage was carried out one year later,

CASE NO. 54.

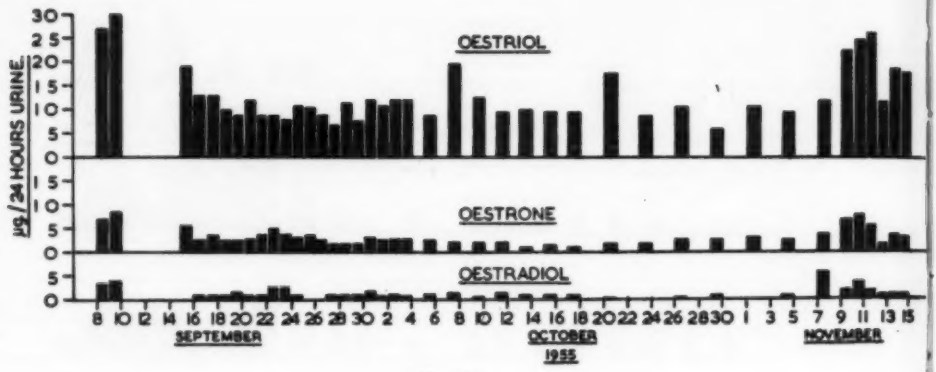

FIG. 26

Case No. 54. Amenorrhoea. Congenital absence of uterus and vagina.

CASE NO. 56.

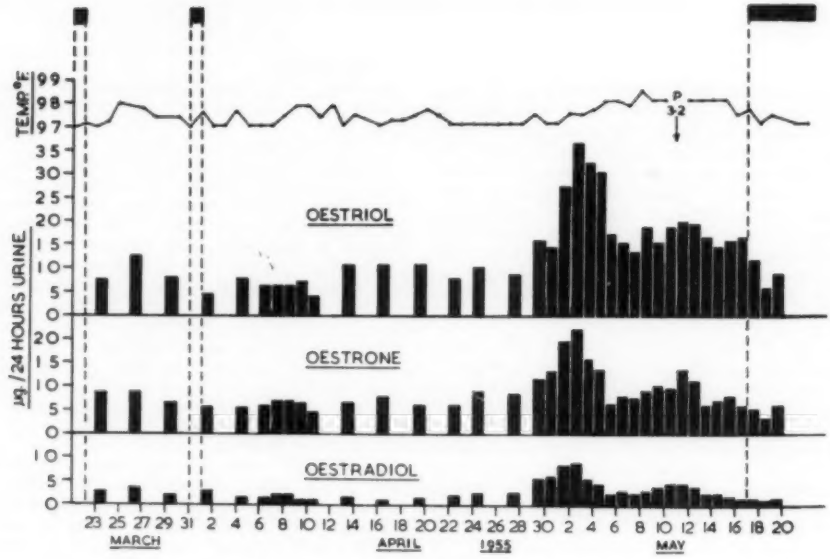

FIG. 27

Case No. 56. Amenorrhoea. Secondary.
(P = Pregnanediol mg./24 hours urine.)

on 3rd February, 1954. The histological picture was that of cystic glandular hyperplasia. Amenorrhoea continued and curettage was repeated on 18th February, 1955 with the same histological findings. A second laparotomy was performed on 22nd April, 1955 when a right combined granulosal and thecal celled ovarian tumour was removed. Three×24 hours urinary collections were made before the laparotomy in 1955 with the following results: Range: oestriol 3·5 μg. to 6·3 μg. (mean 5·0 μg.); oestrone 6·0 μg. to 10·4 μg. (mean 8·2 μg.); oestradiol nil to nil (mean nil); total 9·5 μg. to 16·5 μg. (mean 13·2 μg.). This was an interesting case in that a period of amenorrhoea lasting for 3 years was associated with an endometrium showing cystic glandular hyperplasia. The urinary oestrogens were in keeping with proliferative phase levels and the assumption is that the functioning tumours produced sufficient oestrogens to inhibit the pituitary and thus prevent normal cyclical changes in the ovaries. There is at present no explanation for the amenorrhoea which existed in this case in association with cystic glandular hyperplasia of the endometrium and proliferative levels of oestrogens.

Case No. 56 (Fig. 27). Aged 29 years. Para 0+0. Since the onset of menstruation at the age of 13 years there was gross irregularity of the menstrual cycle. Menstruation occurred at intervals of 8 to 12 weeks. Oestrogen assays were commenced in March, 1955 at which time the history revealed that the last menstrual period commenced on 31st January, 1955 when a first day endometrial biopsy showed proliferative changes. There was slight vaginal bleeding for less than a day on 21st March, 1955 and 31st March, 1955. From 23rd March, 1955 until 28th April, 1955 the total oestrogen levels were within the range 12 μg. to 25 μg. per day. These levels are found during the proliferative phase of the cycle or during anovulatory cycles. However, on 2nd May, 1955 there was a rise of oestrogen levels to an ovulation peak, occurring after a very prolonged proliferative phase, and thereafter the results were in keeping with a normal luteal phase culminating in menstruation on 17th May, 1955. Confirmatory evidence of ovulation was provided by a sustained rise in basal body temperature and an increase in the urinary pregnanediol levels (Fig. 27).

Case No. 57. Aged 37 years. Para 2+0. Menstruation commenced at the age of 13 years and, apart from the interruption of two pregnancies, was regular until 16 months prior to admission. During this period there was complete amenorrhoea and a late symptom was pelvic pain. Examination revealed the presence of a left ovarian tumour. A provisional diagnosis of functioning ovarian tumour was made and confirmed by laparotomy on 31st May, 1955 when a left combined granulosal and thecal celled tumour was removed. Diagnostic curettage performed on 20th May, 1955 provided endometrial tissue showing the very early secretory changes of subnuclear vacuolation. Only 1×24 hours urinary collection was submitted for oestrogen assay on 24th to 25th May, 1955 and the results were: oestriol 9·4 μg.; oestrone 2·4 μg.; oestradiol 0·9 μg.; total 12·7 μg. It is not possible to draw any conclusions from this single urinary assay but it is clear that the readings obtained are not in keeping with a luteal phase which was to be expected from the endometrial findings obtained by curettage carried out 4 days previously. All that can be said in this case is that the presence of the functioning tumour clearly upset the normal cyclical rhythm of the ovaries and in consequence the cyclical changes in the endometrium.

Case No. 58. Aged 34 years. Para 0+0. From the age of 12 years until 21 years menstruation was regular. Thereafter no spontaneous menstruation occurred. Thus, at the time of investigation, amenorrhoea had lasted for 13 years. In June, 1955 3×24 oestrogen assays were carried out. Results: oestriol 1·3 μg. to 3·0 μg. (mean 2·2 μg.); oestrone 1·6 μg. to 3·3 μg. (mean 2·4 μg.); oestradiol nil to 1·3 μg. (mean 0·7 μg.); total 4·6 μg. to 5·9 μg. (mean 5·3 μg.). These figures are clearly within the post-menopausal range and follow-up of this case for 3 years revealed no spontaneous menstruation. This was evidently a case of menopause praecox.

Case No. 59. Aged 21 years. Para 0+0. This was a case of primary amenorrhoea and there was minimal development of secondary sex characteristics. The case was investigated in 1955 when 2×24 hours urinary collections were assayed, with the following results: Range: oestriol 3·1 μg., 5·0 μg. (mean 4·0 μg.); oestrone 3·0 μg., 4·2 μg. (mean 3·6 μg.); oestradiol 0·8 μg., 1·2 μg. (mean 1·0 μg.); total 7·3 μg., 10·0 μg. (mean 8·6 μg.). These figures come within post-menopausal levels and in the follow-up there was no spontaneous menstruation during a period of 3 years. All the circumstances associated with this case suggest that spontaneous menstruation is unlikely to occur but is clearly the type of case which should have further investigation, particularly of pituitary gonadotrophin levels.

Case No. 60. Aged 38 years. Para 0+0. Since the onset of menstruation at the age of 15½ years, cycles were grossly irregular with intermittent short periods of amenorrhoea up to 16-weeks duration. At the time of investigation in 1955 there had been amenorrhoea for 16 weeks. Oestrogen assays were carried out on 4×24 hours urinary collections with the following results: Range: oestriol 2·4 μg. to 3·2 μg. (mean 2·9 μg.); oestrone 1·0 μg. to 4·7 μg. (mean 2·9 μg.); oestradiol nil to nil (mean nil); total 3·4 μg. to 7·9 μg. (mean 5·8 μg.). These figures are within post-menopausal limits and in the follow-up there was no spontaneous menstruation for 3 years. This appeared to be a case of menopause praecox.

Case No. 61. Aged 21 years. Para 0+0. The menarche occurred at 14 years and thereafter menstruation was regular until the age of 20 years, apart from a period of amenorrhoea lasting for 8 months in 1953, at the age of 18 years. At the time of investigation in 1955 amenorrhoea had lasted for 10 months.

Oestrogen assays were carried out on 2×48 hours urinary collections with the following results: Range: oestriol 2·0 μg., 2·5 μg. (mean 2·3 μg.); oestrone 4·1 μg., 4·7 μg. (mean 4·4 μg.); oestradiol 1·8 μg., 3·1 μg. (mean 2·4 μg.); total 9·8 μg., 8·4 μg. (mean 9·1 μg.). The readings in this case are within the post-menopausal range and, therefore, the assumption is that spontaneous menstruation is unlikely. In the follow-up there has been no spontaneous menstruation up to date.

Case No. 62. Aged 18 years. Para 0+0. This patient was of small stature and showed poor development of secondary sex characteristics. There was the history of 2 menstrual periods at the age of 16 years. Thereafter there was no spontaneous menstruation so that, at the age of 18 years, when investigated, there had been amenorrhoea for 2 years. During October, 1955, 3×24 hours and 2×48 hours urinary collections were made and the results of oestrogen assays were as follows: Range: oestriol 10·3 μg. to 15·1 μg. (mean 12·9 μg.); oestrone 3·6 μg. to 4·4 μg. (mean 4·1 μg.); oestradiol 2·1 μg. to 3·3 μg. (mean 2·6 μg.); total 16·7 μg. to 22·1 μg. (mean 19·6 μg.). These readings are clearly above post-menopausal levels and are consistent with functioning ovaries. In the follow-up of this case there was the history of menstrual periods in June and August, 1956 but no further spontaneous menstruation since.

Case No. 63 (Fig. 28). Aged 23 years. Para 0+0. Since the menarche at 15 years menstrual periods had occurred at grossly irregular intervals of 2 to 8 months. At the time of investigation in November, 1955 amenorrhoea had been present for 3 months and an endometrial biopsy performed on 17th November, 1955 showed endometrium in an early proliferative phase. Urinary oestrogen assays were carried out from 18th November until 9th December, 1955 and these are illustrated in Figure 28. From 18th November until 2nd December, 1955 oestrogen levels were extremely

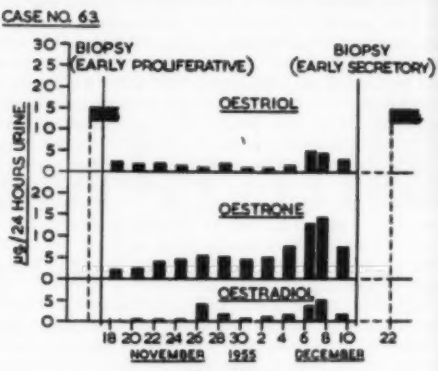

FIG. 28

Case No. 63. Amenorrhoea. Secondary.

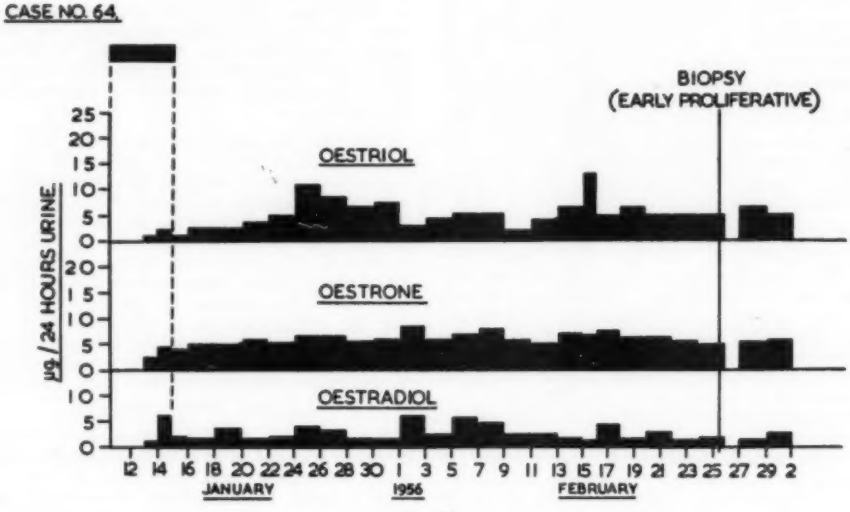

FIG. 29

Case No. 64. Amenorrhoea. Secondary.

low but thereafter increased until a peak was reached on 7th December, 1955. The chart suggests ovulation at this time and confirmation of this interpretation was obtained by biopsy carried out on 11th December, 1955 which showed early secretory changes in the endometrium and on 22nd December, 1955 or 15 days after the ovulation peak, menstruation commenced.

Case No. 64 (Fig. 29). Aged 16 years. Para 0+0. Since the onset of menstruation at the age of 13 years, menstrual periods had occurred at irregular intervals. This patient was admitted to hospital for investigation in January, 1956 but before urinary collections were commenced a menstrual period took place, from 11th to 14th January. From Figure 29 it will be seen that daily urinary oestrogen assays were carried out from 13th January to 25th February, 1956 and from 27th February until 1st March, 1956. In all, 46×24 hours urinary specimens were assayed over this period and the assay results were: Range: oestriol 2·1 μg. to 13·0 μg. (mean 5·6 μg.); oestrone 5·3 μg. to 8·3 μg. (mean 6·3 μg.); oestradiol 1·2 μg. to 6·4 μg. (mean 2·8 μg.); total 9·8 μg. to 22·4 μg. (mean 14·7 μg.). These levels are consistent with endometrial stimulation in the proliferative phase and biopsy carried out on 25th February, 1956 showed early proliferative changes in the endometrium. After investigation this patient was given hormone therapy which resulted in withdrawal bleedings but the first subsequent spontaneous menstrual period occurred in October, 1956.

Case No. 65. Aged 36 years. Para 2+0. From the age of 13 years a regular menstrual rhythm was interrupted on 2 occasions by pregnancies in 1945 and 1946. The last menstrual period occurred in 1952 and thereafter there was amenorrhoea for 4 years prior to investigation in June, 1956. Two×48 hours urinary collections were examined and the oestrogen levels were: oestriol 2·8 μg., 3·4 μg.; oestrone 2·8 μg., 2·3 μg.; oestradiol nil, nil; total 5·6 μg., 5·7 μg. At the same time biopsy failed to produce any endometrial tissue. The figures obtained upon oestrogen assay fell within post-menopausal limits and in the follow-up of this case there has been no spontaneous menstruation to date. The patient has complained of flushes and it is probable that a premature menopause has occurred.

Case No. 66. Aged 20 years. Para 0+0. The menarche occurred at 12 years and until the age of 17 years menstruation was regular. Thereafter for 2 years menstrual periods occurred at irregular intervals and for the 10 months prior to investigation in October, 1956 there was complete amenorrhoea. Only 1×48 hours urinary collection was examined and the oestrogen findings were: oestriol 1·8 μg.; oestrone 3·1 μg.; oestradiol nil; total 4·9 μg. At the same time biopsy failed to produce any endometrial tissue. These oestrogen levels are within the post-menopausal range indicating an absence of ovarian function. In the follow-up of this case there has been no spontaneous menstruation to date.

Case No. 67. Aged 26 years. Para 0+0. From the menarche at 13 years, menstruation occurred at grossly irregular intervals ranging between 6 to 12 weeks, until the age of 23 years. From then until the time of investigation in December, 1956, a period of 3 years, there was complete amenorrhoea. Three×48 hours urinary collections were made between 11th and 17th December, 1956 and subjected to oestrogen assay. The results were: Range: oestriol 15·3 μg. to 18·0 μg. (mean 16·3 μg.); oestrone 5·2 μg. to 6·2 μg. (mean 5·8 μg.); oestradiol 2·0 μg. to 3·3 μg. (mean 2·5 μg.); total 23·5 μg. to 25·4 μg. (mean 24·6 μg.). These are stimulating levels of oestrogen indicating ovarian function. The endometrium was not investigated in this case but spontaneous menstruation occurred on 7th January, 1957.

Case No. 68 (Fig. 30). Aged 26 years. Para 0+0. From the age of 13 years menstruation was regular at 28-days intervals until 10 months prior to investigation. From then there was complete amenorrhoea. The patient was grossly obese and examination under anaesthesia on 2nd February, 1957 showed enlarged cystic ovaries and evidence of uterine hypoplasia. Curettage at this time failed to produce endometrial tissue. Oestrogen assays were carried out between 27th January and 26th February, 1957. In all, 10×48 hours urinary collections were examined with results illustrated in Figure 30. Spontaneous menstrual bleeding commenced on 21st February, 1957 and lasted for 7 days. During the period of assay prior to menstruation the level of total oestrogens was in the region of 12 μg. to 24 μg. (mean 19 μg.). These were stimulating levels but there was no evidence of an ovulation peak, thus the assumption is that the bleeding which commenced on 21st February, 1957 was of an anovulatory type.

Case No. 69. Aged 41 years. Para 1+0. Since the menarche at 13 years the menstrual cycle was

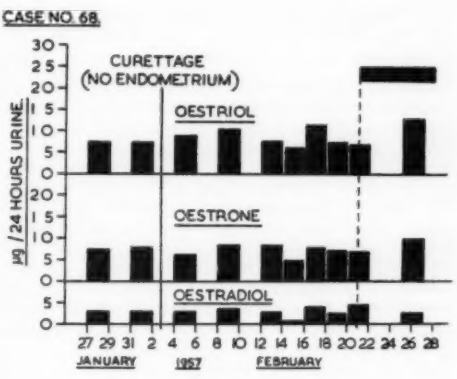

FIG. 30

Case No. 68. Amenorrhoea. Secondary.

entirely regular until one year prior to investigation, with only one interruption due to pregnancy at 25 years. At the age of 40 years there was a period of amenorrhoea for 3 months, then a normal menstrual period followed by amenorrhoea again for 3 months. This was followed by another normal menstrual period in August, 1956 since when there was no menstruation up until the time of admission. On this occasion amenorrhoea had existed for 5 months. Between 7th and 15th February, 1957, 4×48 hours urinary collections were subjected to oestrogen assay. The results were: oestriol 12·0 μg., 16·1 μg., 21·6 μg., 24·8 μg.; oestrone 8·4 μg., 11·2 μg., 12·6 μg., 13·6 μg.; oestradiol nil, 2·8 μg., 2·2 μg., 0·8 μg.; total 20·4 μg., 30·1 μg., 36·4 μg., 39·2 μg. These figures are consistent with oestrogen levels rising to an ovulation peak and this interpretation was supported by a biopsy carried out on 8th February, 1957 which showed a late proliferative endometrium. Subsequent menstruation occurred at the beginning of March and on 8th April, 1957.

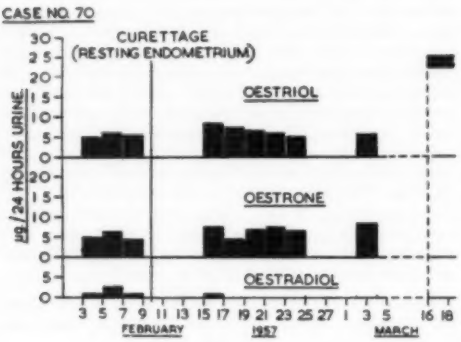

FIG. 31

Case No. 70. Amenorrhoea. Secondary.

Case No. 70 (Fig. 31). Aged 27 years. Para 0+0. Menstruation did not start until the age of 17 years and thereafter was somewhat irregular with occasionally missed periods. On examination there was evidence of hypoplasia of the uterus. Prior to investigation there was a period of amenorrhoea of 6-months duration. Between 3rd February and 3rd March, 1957, 9×48 hours urinary collections were submitted for oestrogen assay. Curettage was performed on 9th February, 1957 when the endometrium was in an inactive resting phase. The results of oestrogen assay, as illustrated in Figure 31 were: Range: oestriol 5·1 μg. to 8·8 μg. (mean 6·3 μg.); oestrone 5·4 μg. to 7·7 μg. (mean 6·2 μg.); oestradiol nil to 2·4 μg. (mean 0·7 μg.); total 11·0 μg. to 17·0 μg. (mean 13·2 μg.). These readings are indicative of ovarian function and are consistent with moderate endometrial stimulation. Menstruation occurred on 16th March, 1957 or 13 days after the last oestrogen assay. It was not ascertained whether this was a normal or anovulatory type of bleeding.

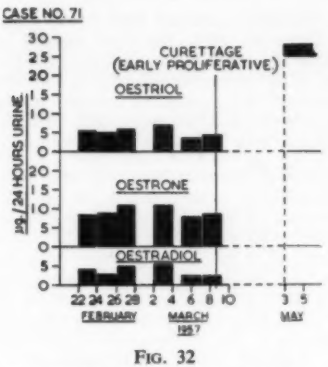

FIG. 32

Case No. 71. Amenorrhoea. Secondary.

Case No. 71 (Fig. 32). Aged 19 years. Para 0+0. From the menarche at the age of 13 years, menstruation occurred at irregular intervals of 2 to 5 months. The patient was grossly obese. Immediately prior to investigation, amenorrhoea had existed for 7 months. Between 22nd February and 9th March, 1957, 6×48 hours urinary collections were investigated and the results are illustrated in Figure 32. Over the period under investigation, the range of oestrogens was: oestriol 4·4 μg. to 7·2 μg. (mean 5·4 μg.); oestrone 7·8 μg. to 11·4 μg. (mean 9·4 μg.); oestradiol 2·5 μg. to 5·5 μg. (mean 3·8 μg.); total 14·1 μg. to 24·1 μg. (mean 18·6 μg.). These levels are consistent with ovarian function and moderate stimulation of the endometrium. Curettage, carried out on 9th February, 1957 showed early proliferative changes in the endometrium and a menstrual period occurred on 3rd May, 1957. It was not ascertained whether this was normal or anovulatory menstruation.

Case No. 72. Aged 21 years. Para 0+0. From the onset of menstruation at the age of 12 years, the menstrual cycle was regular until 1950 (aged 14 years). Thereafter there was a menstrual period in July, 1951 and another in June, 1955. When investigation was carried out in February, 1957, amenorrhoea had been present for 20 months. During February, 1957, 7×48 hours urinary collections were submitted for oestrogen assay. The results were: Range: oestriol nil to 2·3 μg. (mean 0·8 μg.); oestrone 1·2 μg. to 3·3 μg. (mean 2·2 μg.); oestradiol nil to 1·0 μg. (mean 0·1 μg.); total 1·8 μg. to 6·2 μg. (mean 3·1 μg.). These figures correspond to post-menopausal levels. They indicate absence of ovarian function and at curettage performed on 21st September, 1956 no endometrial tissue was obtained. In the follow-up of this case there has been no spontaneous menstruation to date.

Case No. 73. Aged 24 years. Para 0+0. From 11 years of age menstruation was regular until the age of 17 years. Since then there had been no further menstruation. When investigation was carried out in April, 1957, amenorrhoea had been present for 7 years. During April and May, 1957, 3×48 hours urinary collections were submitted for oestrogen assay and the results were: Range: oestriol 1·5 μg. to 5·1 μg. (mean 3·6 μg.); oestrone 2·3 μg. to 4·1 μg. (mean 3·3 μg.); oestradiol 0·6 μg. to 1·3 μg. (mean 0·9 μg.); total 6·2 μg. to 8·9 μg. (mean 7·8 μg.). These figures are consistent with post-menopausal levels. Curettage performed on 25th April, 1957 failed to produce any endometrial tissue and there has been no recurrence of menstruation to date. Thus there is no evidence of ovarian function and the assumption is that this is a case of menopause praecox.

Case No. 74. Aged 28 years. Para 0+0. From the age of 14 years menstruation was regular until June, 1956. Thereafter there was no further menstruation up to the time of investigation in May, 1957. Thus there had been amenorrhoea for 11 months. In this case severe emotional upset may have been a factor in the aetiology of the amenorrhoea. In May and June, 1957, 3×48 hours urinary collections were subjected to oestrogen assay with the following results: Range: oestriol 5·5 μg. to 4·0 μg. (mean 4·5 μg.); oestrone 2·5 μg. to 3·4 μg. (mean 2·9 μg.); oestradiol nil to 0·9 μg. (mean 0·4 μg.); total 6·8 μg. to 8·9 μg. (mean 7·8 μg.). These figures come within the post-menopausal range and curettage carried out on 1st June, 1957 failed to produce any endometrial tissue. The results indicated absence of ovarian function but in the follow-up of this case it was found that menstruation occurred in September, October and November, 1957 and conception took place after the November menstrual period. Although it would be unwise to draw any definite conclusions from such a short-term period of oestrogen assay, this case would appear to suggest that a state of abnormal ovarian function is not necessarily irreversible. In a case of this type it would be helpful to have a knowledge of pituitary gonadotrophin output.

Case No. 75. Aged 18 years. Para 0+0. Menstruation did not commence until the age of 17 years and thereafter occurred at irregular intervals for 7 months only. When admitted for investigation, amenorrhoea had lasted for 4½ months. During October, 1957, 4×24 hours urinary collections were subjected to oestrogen assay. The results were: Range: oestriol 7·2 μg. to 9·0 μg. (mean 8·2 μg.); oestrone 3·6 μg. to 5·2 μg. (mean 4·2 μg.); oestradiol 0·5 μg. to 1·9 μg. (mean 1·1 μg.); total 12·4 μg. to 14·3 μg. (mean 13·5 μg.). These levels are consistent with moderate oestrogenic stimulation of the endometrium and curettage carried out on the last day of urinary collection showed endometrium in an early proliferative phase. The immediate post-investigation period was confused by the administration of hormone therapy but spontaneous menstruation subsequently occurred on 31st December, 1957 and regularly thereafter.

This series of cases of amenorrhoea can be divided up into groups according to the assay findings and subsequent history.

In Group I, Cases Nos. 52, 53 and 54, the cause of primary amenorrhoea was congenital absence of uterus and vagina. Urinary oestrogen assay over a prolonged period showed evidence of cyclical ovarian function in each case and thus proof has been provided that normal ovarian function is possible in the absence of the target organ, the uterus.

Group II consists of 8 cases, one with primary amenorrhoea (Case No. 59) and 7 with secondary amenorrhoea (Cases Nos. 58, 60, 61, 65, 66, 72 and 73). In all of these cases the oestrogen levels were within post-menopausal limits. In the subsequent follow-up of these patients spontaneous menstruation did not occur over periods ranging from 1 to 3 years. In this group of 8 cases the oestrogen range was: oestriol nil to 5·0 μg. (mean 2·4 μg. ±1·1 μg.*); oestrone 1·0 μg. to 4·7 μg. (mean 3·2 μg. ±0·6 μg.*); oestradiol nil to 3·1 μg. (mean 0·7 ±0·9 μg.*); total 1·8 μg. to 10·0 μg. (mean 6·3 μg. ±2·0 μg.*). These figures resemble very closely those for the post-menopausal patients with inactive endometrium included in the section of this paper devoted to cases of post-menopausal bleeding (Section I, Group I). Although the ages of the patients in this group range from 20 to 38 years the clinical and assay evidence suggests an absence of ovarian function to a degree consistent with post-menopausal changes. Thus it would be reasonable to conclude that these are instances of menopause praecox. However, it is necessary to strike a note of caution, particularly in relation to short-term oestrogen assay, as Case No. 74 illustrates the apparent reversibility of such a situation. From these observations it is clear that a dogmatic opinion cannot be given unless oestrogen assays are carried out over a prolonged period of, perhaps, at least 3-weeks duration. It may be that the finding of post-menopausal levels of oestrogen in the urine of patients within the child-bearing age period is capable of at least two explanations. Firstly, it is possible that the ovaries in these cases may

* Standard deviation.

contain no follicles capable of maturation or function. In such cases the situation is irreversible. On the other hand, in other cases there may be temporary suppression of ovarian function for variable periods of time. In extreme examples the urinary oestrogens may fall to post-menopausal levels but the situation is reversible and return of function may occur spontaneously or as the result of therapy. It is clear that this type of case demands further investigation especially with regard to aetiology, and particularly with reference to the role of the pituitary. Cases of this type are at present being investigated along these lines.

Group III consists of 2 patients, Cases Nos. 63 and 74. In each of these, amenorrhoea had lasted for several months and after a long period of insufficient oestrogen output there was evidence of spontaneous recurrence of ovarian function with ultimate ovulation and menstruation.

Group IV consists of 2 patients with functioning ovarian tumours, Cases Nos. 55 and 57. In both of these cases the urinary oestrogen levels were, perhaps surprisingly, low in that they were consistent with somewhat low proliferative levels. It is probable that the continuous supply of oestrogens from the tumour, without progesterone, is sufficient to inhibit the pituitary which, in turn, suppresses normal ovarian function. At the same time, the oestrogen levels are sufficient to maintain proliferative changes in the endometrium.

Group V consists of the remaining 9 patients who showed evidence of varying degrees of ovarian function. Cases Nos. 62, 64, 67, 68, 70, 71 and 75 were associated with proliferative phase levels of urinary oestrogens. They are thus examples of partial temporary suppression of ovarian function and, as such, justify further investigation including assay of pituitary gonadotrophins. In each of these cases spontaneous menstruation subsequently occurred but it was not ascertained if this was associated with ovulation or not. Cases Nos. 56 and 69 were somewhat similar, but in each of these cases there was clear evidence of ovulation occurring after 4- and 6-months amenorrhoea respectively.

Discussion

This study covers a miscellaneous collection of gynaecological disorders. Each case has been summarized with details of clinical and pathological data and results of oestrogen assay. The various findings have been interpreted in relation to individual patients or to groups of similar cases. Thus it would be needlessly repetitive to embark upon a detailed discussion of all cases again. In many instances, investigation was far from complete and additional information would have been desirable. However, it is possible to draw some general conclusions from the results. Taking a broad view it would appear that the pattern of urinary oestrogen excretion follows one of two trends. The first trend (Type I) consists of those patients who show a more or less constant level of urinary oestrogens and includes post-menopausal patients and cases of amenorrhoea with inactive endometrium, patients exhibiting anovulatory cycles and some cases of cystic glandular hyperplasia. In the second trend (Type II) the levels of urinary oestrogens show marked periodic fluctuations. Into this category would fall those patients with ovulatory cycles and some cases of cystic glandular hyperplasia. In these patients the variations in urinary oestrogen levels are presumably due to maturation and regression of follicles, normal or abnormal. Ovulation, itself, is invariably associated with a demonstrable rise and fall in oestrogen levels (the ovulatory peak).

Type I (Fig. 33). Constant Oestrogen Levels

Patients falling within this category may be classified according to the degree of endometrial proliferation as it is seen that the histological pattern of the endometrium is closely correlated with the level of oestrogens excreted in the urine.

(1) *Atrophic Endometrium.* This group includes the post-menopausal cases Nos. 1 to 10 and the cases of amenorrhoea Nos. 65, 66, 72 and 73. In each of these patients urinary oestrogen excretion was less than 10 μg. total oestrogens/24 hours.

(2) *Early Proliferative Endometrium.* The cases comprising this group, Nos. 18, 19, 21, 64 and

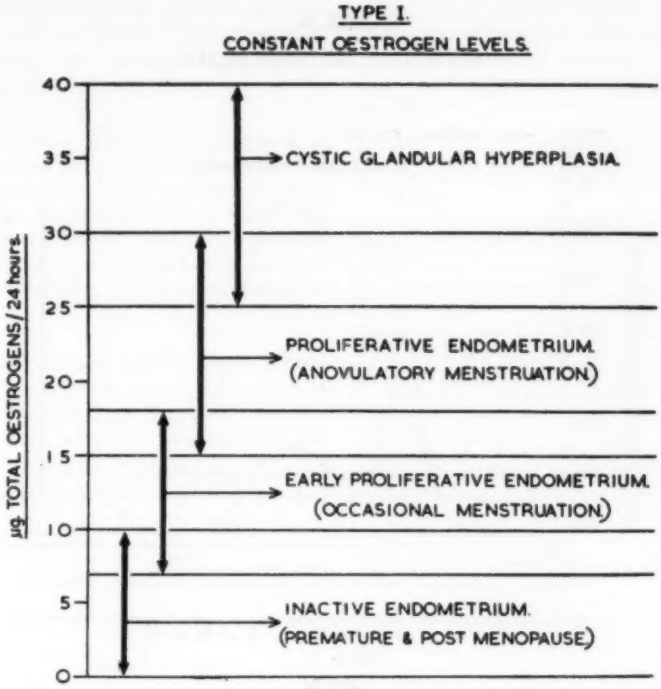

FIG. 33

Correlation between oestrogen levels and endometrial pattern.

75, each exhibited occasional phases of bleeding and excreted between 7 and 18 μg. total oestrogens/24 hours.

(3) *Proliferative Endometrium.* Into this group fall the patients with proven anovulatory menstrual cycles, Cases Nos. 24 to 29. During these cycles the total daily urinary oestrogen excretion fell between 15 μg. and 30 μg. At these levels bleeding occurred at more or less regular monthly intervals.

(4) *Cystic Glandular Hyperplasia.* This group comprises some of the cases with the clinical diagnosis of Metropathia Haemorrhagica and the histological endometrial picture of cystic glandular hyperplasia. Typical examples are provided by Cases Nos. 30 and 38. In these patients between 25 μg. and 40 μg. total oestrogens were excreted daily in the urine.

There is a certain amount of overlap between the oestrogen levels found in each of the above subdivisions (Fig. 33). This is not surprising when account is taken of several individualistic variable factors such as endometrial response and duration of endometrial stimulation.

Type II (Fig. 34). Fluctuating Oestrogen Levels

In the second category are included those patients who exhibit fluctuating oestrogen levels and these cases can again be subdivided according to the endometrial pattern.

(1) *Secretory Endometrium.* (Normal cycle.) The urinary oestrogen excretion pattern is characterized by the occurrence of two peaks, between episodes of bleeding from a secretory endometrium. The first rise produces the "ovulatory peak" and the second the "luteal

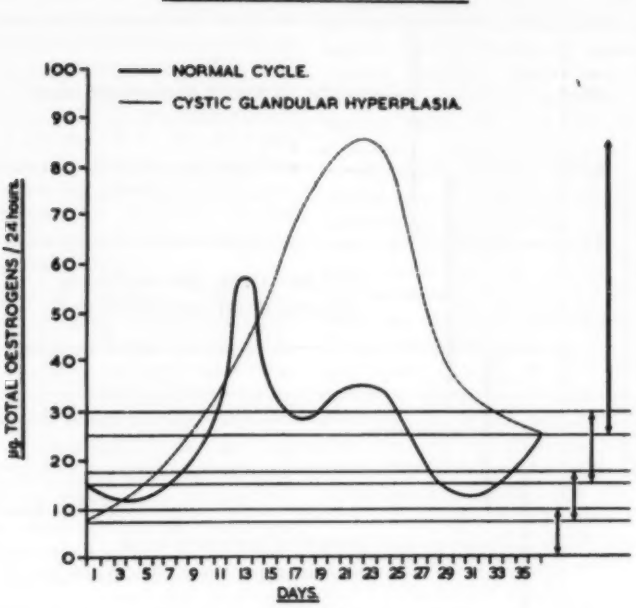

FIG. 34

maximum". Menstrual bleeding occurs shortly after the luteal maximum and approximately 14 days after the ovulatory peak. The luteal maximum is associated with progesterone production by the corpus luteum.

(2) *Cystic Glandular Hyperplasia.* Some of the cases with proven cystic glandular hyperplasia come into this category and typical examples are provided by Cases Nos. 31 and 32. These cases showed a rise and fall of oestrogen levels between episodes of bleeding. The elevated levels were maintained for a longer period of time, and were usually greater, than those associated with the ovulatory peak of the normal cycle. Under these conditions uterine bleeding occurred whilst the oestrogen levels were rising, at the elevated levels, or whilst they were falling.

The patterns of oestrogen levels in these two subdivisions are illustrated in Figure 34 which incorporates the applicable features of Figure 33. It should be noted how constantly oestrogen levels are related to endometrial pattern.

SUMMARY

(1) The urinary excretion of the three oestrogens, oestriol, oestrone and oestradiol-17β has been measured in 75 patients suffering from a variety of gynaecological disorders.

(2) The results have been correlated with the histological appearance of the endometrium and with phases of uterine bleeding. Readings have also been compared with those in women with normal menstrual cycles and with those in women beyond the menopause.

(3) A direct correlation was found between the histological state of the endometrium and the levels of urinary oestrogens.

(4) It was found that the various gynaecological states could be subdivided into two main types depending on whether constant or fluctuating amounts of oestrogens were being excreted.

(5) It is clear that, although a great deal of useful information can be derived from urinary oestrogen assay alone, it is essential to relate those results to the levels of other hormones, particularly progesterone and the gonadotrophins, in order to assess and treat cases of dysfunctional bleeding in the gynaecological patient.

The authors wish to acknowledge the invaluable assistance of the many technicians of the Clinical Endocrinology Research Unit and the Department of Obstetrics concerned in this study. Thanks are due to those clinical colleagues who made available cases for investigation and to Dr. Arnold Klopper who provided particulars of pregnanediol assays. This study would not have been possible without the willing and untiring co-operation of nursing staff and patients.

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SYNCHRONOUS COMBINED ABDOMINO-VAGINAL HYSTEROCOLPECTOMY FOR CANCER OF THE CERVIX—A REPORT OF FIFTY PATIENTS

BY

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A SHORT account of the synchronous combined abdomino-vaginal operation for carcinoma of the cervix was published by the author in 1951. No originality was claimed for the method which was the logical application of the Lloyd Davies technique to a purely gynaecological problem. Ameline, Huguier, Moÿse and Chatain must have had the same idea at about the same time and, in their monograph, *La Chirurgie à Deux Équipes dans le Traitement des Cancers Pelviens* (1950), they describe the synchronous method as applied to cancer of the bladder, rectum and cervix. Mr. D. W. Currie informs me that Carlton Oldfield, many years ago, operated on certain carcinomata of the cervix by a combined but not synchronous abdominal and vaginal technique and many other mute inglorious surgeons must have performed this obvious operation.

In 1947, the late Wilfred Shaw and I performed the first synchronous combined operation in this series and the patient is alive and free from recurrence 11 years after the operation. Since then, with many assistants ranging from consultant to registrar, the operation has been undertaken on all types and grades of pelvic cancer, several of which do not appear in this paper because they were complicated either by anterior or total exenteration. It has been thought proper to exclude these extra-genital operations since they automatically load the mortality and morbidity figures and this paper is, therefore, confined to 50 patients in whom histologically proved invasive cancer of the cervix was treated by radical hystero-colpectomy. Without exception, all the patients in this series have been treated by pure surgery and no pre-operative or post-operative radiation has been used. This paper is an attempt to assess the scope, mortality and morbidity of the operation.

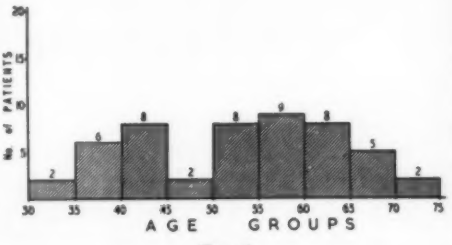

FIG. 1

Age group of the fifty patients operated upon.

Incidentally, the synchronous combined approach has been successfully applied to a number of benign conditions such as vesico-vaginal fistula and hernia of Douglas's pouch (Barbut, 1951). In these non-malignant cases, the method has proved of great technical benefit to both surgeon and patient in that a difficult problem, which has its abdominal and vaginal advocates, has been tackled simultaneously from both approaches. The technique has even been extended to certain cases of carcinoma of the vulva in which, using the lithotomy Trendelenburg position, one team has

dissected the iliac glands on each side while a second has removed the primary vulval carcinoma.

The first conclusion to be drawn from these synchronous operations is that the original claim of a wider and better removal of the parametrium and paracolpos is vindicated. Spectators and critics from home and abroad have all consented to this statement. Secondly, growths which by the ordinary Wertheim would be deemed inoperable and inadequately removable, have been made amenable to surgical eradication. Thirdly, the surgical and moral support of an expert assistant working from below has sometimes proved the turning point in an otherwise intolerable situation, and the author would like to acknowledge the timely succour and encouragement of his colleagues which have on several occasions turned defeat into success. Herein lies one of the chief merits of the combined approach. It is most heartening to have an expert assistant who, at a moment's notice, by changing gown and gloves, can be summoned to work in the abdominal field should some unforeseen complication arise which demands exceptional experience. Where large bowel resections are envisaged, it is a great asset to operate with a proctologist and the author has learned much of surgical anatomy and technique from the collaboration of his surgical colleagues.

Pre-Operative Treatment

In my original paper, the unsuitability of small hospitals and nursing homes for the performance of this operation was stressed and increasing experience has amply justified this statement. The only operative death—that is, by definition, a death within 28 days of the operation—occurred in a small institution where faulty management of a drip transfusion resulted in a fatal air embolism 7 hours after the operation. The post-operative safety of the patient depends on the skill of the nursing staff, registrars and housemen and that skill is only acquired by the experience of a large number of similar cases. Moreover, the pathological and biochemical control of these patients has assumed great importance in recent years and the ready availability of highly trained personnel is essential for assessing such features as potassium imbalance, on the accurate correction of which the patient's life may depend.

The blood chemistry of the patient is fully investigated before operation and the haemoglobin level corrected, as necessary. Intravenous urography and cystoscopy are carried out as a routine; it cannot be too emphatically stressed that a full urological investigation is essential. Unsuspected bladder involvement is thereby discovered or suspected and the presence of ureteric obstruction places the surgeon on his guard in prognosis and may alter the scope of his operation entirely. Urinary infection, if present, is corrected and, if bladder extirpation and uretero-colic implantation is envisaged, the bowel is sterilized pre-operatively with streptomycin and/or phthalyl sulphathiazole.

Anaesthesia

Increasing experience with epidural anaesthesia has hardened my original opinion that this is the best anaesthetic at present available and tribute is paid to the skill and patience of Dr. Frankis Evans and Dr. Massey Dawkins. The moderate hypotension induced minimizes oozing and blood loss and the contraction of the bowel ensures a clear unembarrassed pelvic field. In those few cases when, for technical or other reasons, an epidural was not available, it has been sadly missed and what should have been a meticulous and dignified dissection has developed into a bitter and frustrating dog-fight with the intransigent bowel. When using an epidural anaesthetic, it is important to have an intravenous drip transfusion running to combat any tendency to undue hypotension during and after operation. Liberal oxygenation of the vital centres is equally essential.

Operative Technique

The actual technique of the operation follows the classical Wertheim of Bonney, Goodwin and Meigs. The cellular tissue and glands of the retro-peritoneum are cleared from the common, external and internal iliac vessels from above downwards as a first step and displaced medially.

This exposes the ureter and the branches of the hypogastric vessels early and safeguards the ureter at once. The hypogastric vessels can be ligated if necessary at their source though it is usual only to ligate the obliterated hypogastric where the uterine arises. In this way, the lateral pelvic wall is cleared from the adventitia of the external iliac vessels to the levatores ani, only the obturator nerve being left in splendid isolation and this can be sacrificed if need be. The external iliac vein can be removed if malignant glands are inextricably adherent to it. Sometimes a mass of glands surrounds the external iliac artery and, if these cannot be dissected from it, the operation has to be abandoned. In future, this will not necessarily be so since an arterial resection and graft is a perfectly feasible operation and should certainly be attempted in an otherwise suitable case. In performing this lateral dissection of the pelvic wall, a word of warning is timely regarding the venous channels of the hypogastric system. These veins form a complicated network of very easily torn vessels and undue traction upon them may avulse the pudendal and gluteal branches which recoil out of reach of the forceps and give rise to alarming and uncontrollable haemorrhage. At all costs this catastrophe is to be avoided as the blood loss will jeopardize the patient and its control by suture ligature may damage the lumbo-sacral plexus. This complication has only occurred once in the author's experience, and not in this series, but it resulted in a foot drop—the price of securing haemostasis. It is, therefore, prudent to exercise the greatest caution when dissecting and ligating the vessels in this region.

The author has adopted two very useful instruments in the control of pelvic haemorrhage. The first, borrowed from the vascular surgeons, is a temporary haemostatic bulldog clamp applied to one or both common iliac arteries. This very effectively controls arterial bleeding from the branches of the hypogastric artery (Fig. 2). The second instrument used to control inaccessible venous bleeding which is occurring from an easily torn, thin-walled vein of the hypogastric venous plexus is the silver wire clip of the neurosurgeons. The application of these clips is quick, easy and certain and, used in connexion with the sucker, they have proved invaluable. Both these instruments are strongly recommended to any surgeon who performs or contemplates the surgery of pelvic cancer (Fig. 3).

The pouch of Douglas presents certain difficulties which, if not realized, may result in a large bowel fistula. Quite frequently the rectum is looped up and tethered to the anterior wall of the pouch in the region of the upper one-third of the vagina or even the cervix and in opening the peritoneum this fact must be borne in mind. The vaginal operator can be of great help in finding the correct plane of cleavage in the recto-vaginal septum and he should place his finger, guarded by a metal thimble, in the proper space. The rectum can then be freed from above and below and pressed backwards away from the utero-sacral folds and ligaments which can then be clamped and cut well back, but with due respect for the terminal branches of the superior haemorrhoidal arteries which run down each side of the rectum in this position. Damage to these vessels may result in avascular necrosis of the rectum and a fistula difficult to close. The middle haemorrhoidal vessels are of little importance to the bowel and can be ligated with impunity.

The vaginal part of the operation follows Schauta's procedure and only presents real difficulty when the growth has extended far down the vaginal wall. Once the attachment of the pubo-rectalis to the vagina has been severed, the two operators can free the whole mass of the paracolpos and the parametrium from the lateral pelvic wall. If necessary, a considerable part of the pubo-rectalis can be sacrificed as well. During this stage of the operation, the ureter is guarded by the abdominal surgeon.

During the dissection of the bladder from the cervix and vagina, both surgeons should work in conjunction. At the lateral angles of the bladder where the anterior fibres of Mackenrodt's ligament pass forward over the ureter, there is a large piece of ill-defined cellular tissue which should be as widely removed as possible. It is sometimes difficult to know the exact boundaries of the bladder and the surgeon is tempted to make a timid and inadequate dissection. If the

vaginal surgeon fills the bladder at this stage with 8 to 10 ounces of solution, great assistance is given to his abdominal colleague who can then see quite clearly how far he may cut with safety. In this way, a wide and satisfactory excision is achieved.

When the specimen is removed, both surgeons spend a few minutes ligating any residual bleeding points in the depths of the pelvis; it is usually easier for the abdominal surgeon to clamp the vessels while the vaginal surgeon can more easily tie them from below. The cavity is then lined with oiled silk into which gauze is packed and the pelvic peritoneum united with multiple interrupted fine catgut sutures. It is important to ensure that the ureter is gently raised on the upper surface of the pack and not compressed in any way by it. The oiled silk is less liable to cause bleeding on removal whereas gauze without it tends to cause oozing by tearing young granulation tissue and small vessels which adhere to it (Fig. 4).

Post-operative Care. It is now my practice to leave an indwelling catheter in the bladder for 3 weeks, draining without obstruction into a Winchester under the bed. As some may criticize this procedure, the reasons are given in detail. The blood supply of the terminal ureter is derived from the hypogastric artery and its branches, notably a ureteric branch of the uterine (Racker and Braithwaite, 1951; Howkins, 1954), and from the inferior vesical artery. In all Wertheim operations some of these vessels are ligated and it is indeed surprising that the ureter does not slough more often. This danger is especially real if the internal iliac has been tied at its origin. Because of these vascular considerations, the post-operative fate of the ureter must be accepted as always being in the balance. If, therefore, the tenuous blood supply is further embarrassed by the uretero-vesical angulation inherent in a full bladder, an additional insult is heaped upon this already struggling structure. Continuous catheter drainage of the bladder ensures that the uretero-vesical junction is at rest and undistorted and, if a small leak should develop, at least there is no back pressure upon it and healing by granulation is encouraged. It goes without saying that any urinary infection is treated by the antibiotic to which it is sensitive.

The treatment of the bowel is important. Mild oil emulsion aperients such as Milpar can be started on the second or third day but all enemata are absolutely interdicted. As a rule these patients do not unduly suffer from ileus but, if they do, treatment should be by early duodenal aspiration and intravenous infusion.

The pack is best removed under a light anaesthesia or morphine, gr. ¼, in the theatre after forty-eight hours. Later removal is inadvisable as haemorrhage is more likely from tearing small vessels and veins involved in early granulation tissue. The gauze is first removed, leaving the covering of oiled silk *in situ* for a few minutes during which time the cavity is given an opportunity to bleed if it is going to do so. If it does bleed and re-packing is deemed necessary, a new pack can be inserted into the original envelope of oiled silk. This saves unnecessary disturbance of the pelvic contents and greatly facilitates the re-packing. The second pack should not be left in for more than a further 48 hours.

An important aspect of the post-operative care of these patients is the balance of their water and electrolytes. A careful fluid balance chart is kept in 12-hourly periods and the serum sodium, chloride and potassium estimated daily and corrected according to the principles of Le Quesne (1954). The haemoglobin is estimated as clinically required and restored as and when indicated.

Special care is taken to diagnose any phlebothrombosis early but, surprisingly, these big operations are not unduly worrying in this respect.

Should a urinary fistula develop, it is in the first instance treated conservatively and the author's method of double suction drainage is recommended as the best method of keeping the patient dry, cheerful and comfortable. One catheter is placed in the bladder and connected to a low pressure electric suction pump and a second large mushroom catheter is placed in the operation cavity and packed *in situ* with vaseline gauze; this catheter is also connected by a Y-piece connector to the suction pump and removes the fistulous urine. In an extensive

operation of this kind, the motor and sensory nerve supply of the bladder must be almost completely severed and it is remarkable that it ever recovers its function at all (Meigs, 1944, 1950, 1954; Twombly, 1950; Beecham and Emich, 1952; Kebo, 1952; Brunschwig, 1953; Douglas and Birnbaum, 1954; Thornton, 1954; Lewington, 1956). A great number of these patients will, therefore, suffer from retention of urine and will have large residual quantities up to a pint or more after micturition. This need cause no alarm and catheterization two to three times a day will show an ever decreasing quantity. Sometimes this residual urine is persistent and may last for six months or longer. No notice need be taken of this and the patient is sent home in spite of it. She should be seen regularly as an out-patient and given 1 g. of sulphacetamide a day to be taken indefinitely. In one of my patients, this residual urine lasted for more than six months but eventually cleared spontaneously without any treatment. Bladder function is further complicated by loss of sensation so that the patient does not know when the bladder is full. Such patients need very careful education and encouragement before they acquire the necessary technique of starting micturition by contracting their voluntary muscles or even by supra-pubic pressure. It is difficult to know whether sensory or motor loss is the more important factor in such patients and probably both are operative.

A careful follow-up has been personally made of all the 50 cases in this series and this has disclosed a distressing number of urinary complications. All urinary complications have been included and there were 21. Of these, half were mild and transient, and disappeared in a few months, leaving the patient well satisfied with her bladder condition. Eleven, however, have presented a real problem. There were 4 cases of severe stress incontinence, one of which was so bad that a uretero-colic implant was performed successfully; no recurrence was found in this case. One other case of stress incontinence has recently been treated by a Marchetti operation combined with a urethrolysis from the vagina; this, I think, is important as the urethra becomes anchored in dense, hard scar tissue.

TABLE OF URINARY COMPLICATIONS

Complication Rate: 21 out of 50 cases. (This figure includes all cases but is subject to annual review as some improve with time and, with the more recent patients, sufficient time has not yet passed to assess them properly.)

Of the 21:

1—Recto-vaginal fistula—so small as to be symptomless and no operation necessary.

9—Mild or transient stress incontinence—insufficient to warrant treatment or cause the patient much inconvenience. (Of these 3 have now completely recovered and have full control.)

4—Complete incontinence due to incompetence of the urethra. (1 uretero-colic implant; 1 wears a rubber urinal; 2 are being considered for urinary diversion.)

5—Loss of bladder sensation but no incontinence.

2—Recurrence leading to fistula.

Other surgeons who have performed this operation complain of the same problem of stress incontinence and I feel that the low dissection of the vagina from the urethra, and the subsequent fixation of the urethra in scar tissue is somewhat to blame. It is proposed, in future, to leave the lower part of the anterior urethra unless the growth has extended dangerously low in the vagina. It has been pointed out that these extensive operations for cancer of the cervix must deprive the bladder almost completely of its motor and sensory nerve supply and, although surgery can successfully eradicate the malignant growth, it is unsatisfactory if the patient is left with an incompetent bladder as the price of curing the cancer.

The after-care of the cavity in the pelvis is simple. As a rule this heals quite quickly—in a favourable case in 3 weeks. If local sepsis develops, the best treatment is frequent baths and the instillation of 1 ounce of glycerine into the cavity after each bath. After a time, only a small residual space is left unhealed and this can be quite well treated at home by the patient or the district nurse.

IRRADIATION PLUS SURGERY

It has already been mentioned that the author does not employ either pre-operative or post-operative irradiation and, in deference to several experienced surgeons who do use

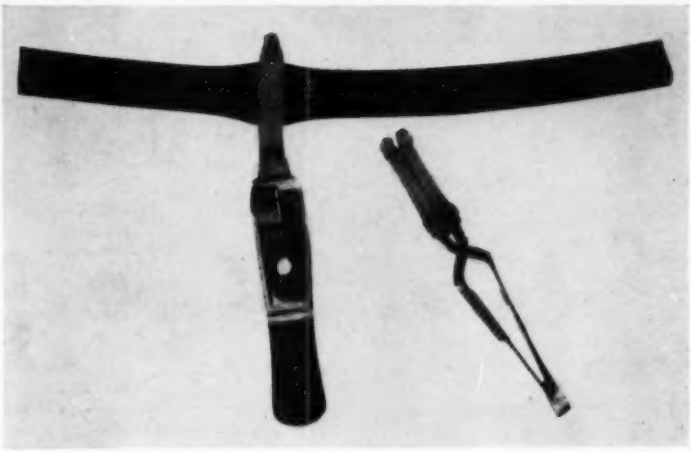

FIG. 2

Blalock's bulldog clamp. This instrument, when applied to both common iliac arteries, enables the surgeon to control arterial haemorrhage in the pelvis. It should only be applied during moments of stress and not left on for longer than necessary.

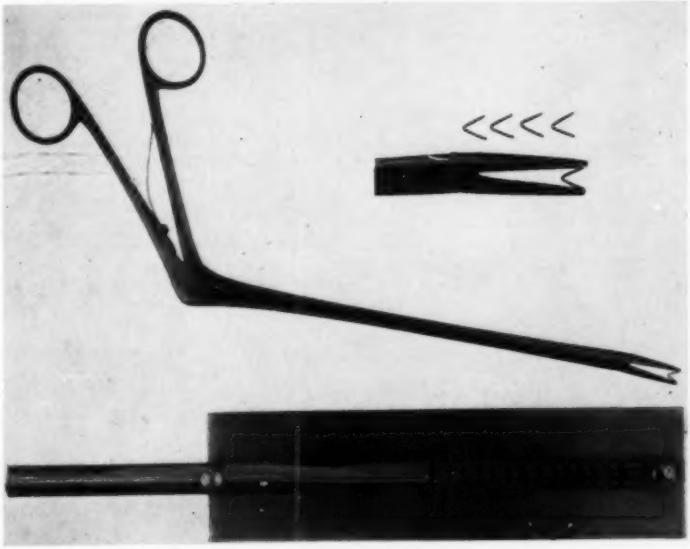

FIG. 3

Paterson's longshank clip forceps. This instrument provides the best method of controlling venous haemorrhage from the tributaries of the hypogastric vein. The author strongly recommends it.

FIG. 4

Typical specimen removed by the synchronous combined operation. Note the generous margin of parametrium and paracolpos. Note, also, that the growth extends halfway down the vagina. This is the situation in which total removal of the vagina is indicated and in which the classical Wertheim would remove an insufficient margin below the growth.

adjuvant irradiation, some reasons are given for the purely surgical approach to this problem.

While it is acknowledged that the pre-operative irradiation will shrink and to some extent sterilize the primary growth, there is a feeling among some surgeons (Berenky, 1950; Way, 1951; Pratt, 1951) that the incidence of urinary and bowel fistula is greater after radiation plus surgery. Moreover, the ultimate fibrosis in the operation site is more liable to cause ureteric obstruction and renal morbidity. It is a debatable point not yet finally decided whether pre-operative radiation increases the technical difficulties of dissection from haemorrhage and cellular reaction and, in the author's limited experience of such cases, the impression has been formed that the operation was more difficult but not significantly so if the timing of the surgical attack was correct—not too soon and not too late after irradiation.

Regarding post-operative irradiation, it is agreed with Meigs (1953) that radiotherapy has nothing to offer in the sterilization of an involved lymphatic field though judgment should be suspended on the newer supervoltage techniques. It is felt, however, that a properly performed lymph node dissection, which is the vital argument of the surgical attack, should remove all involved and potentially involved pelvic nodes and that, therefore, there is nothing left to irradiate. Schlink (1953) has stated that it is the nodes that are important and not a few isolated cancer cells in the cellular tissue and, if this is true, there can be little or no point in offering these patients irradiation. There is some argument that the ultimate long-term morbidity of the ureter and bladder is increased by irradiation and a urographic study of the 5-year cures of radiation should be an instructive investigation. Surgery is not, however, blameless as a cause of late ureteric obstruction and the whole question awaits a full authoritative report on a series of cases treated by pure surgery and a comparable one treated by pure radiation.

It is, perhaps, relevant to mention here one point about radiation which is apt to be overlooked. This is the psychological and, to a lesser extent, the physical effect which radiation produces in the patient. A full course may last up to eight weeks and involves almost daily visits to the treatment room where, sooner or later, the patient is bound to realize that she has joined the "cohorts of the damned". However good the prognosis may be, the certain knowledge that she is a cancer patient cannot be concealed from the recipient of radiation treatment. It was pointed out many years ago by Victor Bonney that the lot of the surgical patient is a far happier one; once she has survived the ordeal of the operation, her treatment is ended and she need never know that she has had anything more than a hysterectomy and can draw whatever comfortable conclusions she wishes.

Pathological Report

The importance of a full and accurate pathological report must be stressed. At St. Bartholomew's Hospital, each specimen is now photographed and a large number of blocks are prepared so that the exact extent of the primary growth can be defined and parametrial and vaginal invasion assessed. The glands are separately labelled as right and left common iliac, external iliac and obturator, and a separate report on each prepared, with the number sectioned and whether invasion has occurred or not. A diagram after the method of Cuthbert Dukes for carcinoma of the rectum has just been prepared and it is hoped in future to provide by such a graphic method material on which to base prognosis and treatment (Fig. 5).

With increasing experience, there is no doubt that the extent of the operation is enlarged and more parametrium has been removed in the later cases than in the first. Apart from widening the anatomical possibilities, several other interesting problems have arisen, the investigation and solution of which are not yet complete. It is fair to say that we now know more about the biochemistry of the patient before and after operation and that our cases are safer than when the series was first begun.

Conclusion

(1) The synchronous combined abdomino-vaginal hysterocolpectomy for carcinoma of the cervix is a feasible proposition and need carry

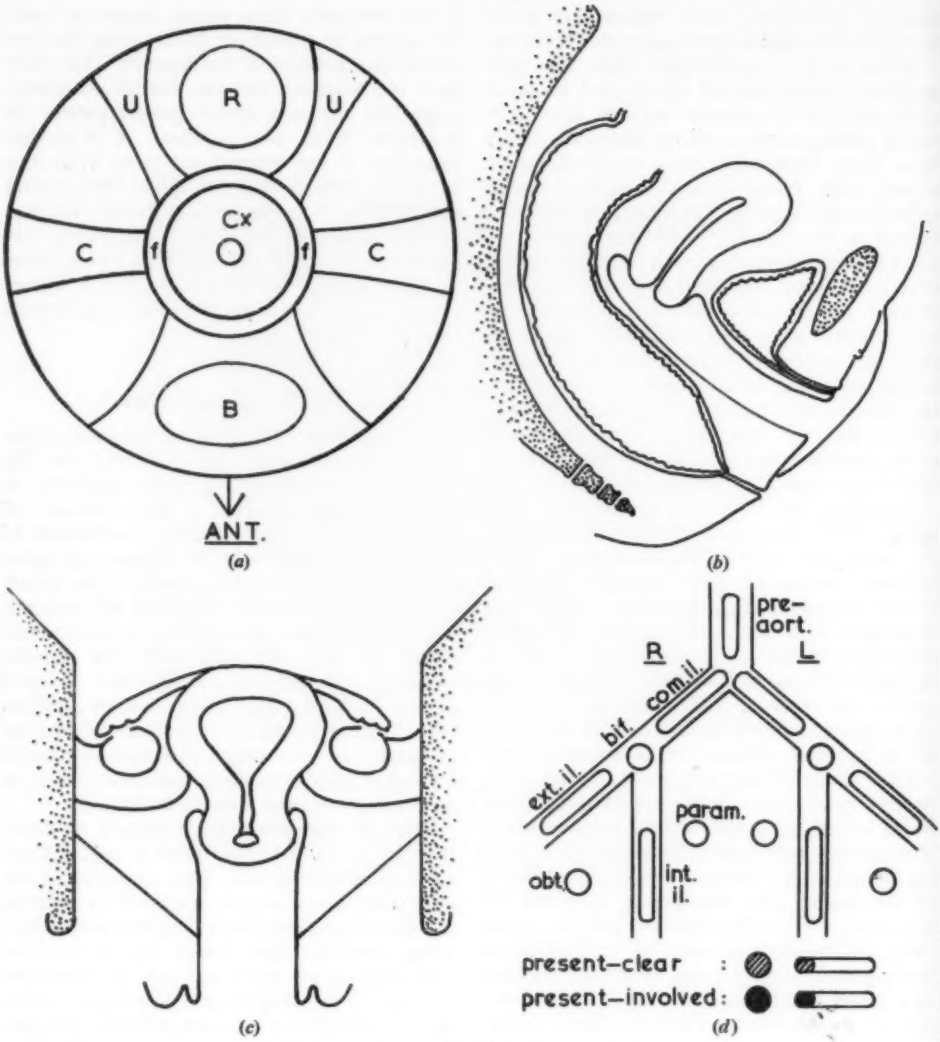

FIG. 5

Diagrams used for records of assessment of carcinoma of the cervix at St. Bartholomew's Hospital.

(*a*) Plan of pelvis at level of cervix, viewed from above:

Cx = cervix C = cardinal ligament.
R = rectum U = utero-sacral ligament.
B = bladder f = lateral fornix.

(*b*) Sagittal section to record anterior and posterior spread.

(*c*) Coronal section to record lateral spread.

(*d*) Diagram incorporated in the pathological report to indicate site and involvement of lymph nodes.

very little greater mortality than the ordinary Wertheim operation. In this series of 50 patients, there was one unnecessary and avoidable death due to a transfusion accident resulting in an air embolism; the patient at autopsy was otherwise completely satisfactory and the operation can in no way be blamed for this fatality.

(2) There can be little argument that the synchronous combined abdomino-vaginal operation is the most extensive yet devised for the removal of a cervical cancer and its potential lymphatic extensions. The criterion of a successful operation is a clean and empty pelvis. bounded above by the external iliac vessels cleared of all glands and cellular tissue, laterally by the naked obturator internus and levator ani muscles, and below by the vaginal introitus. Anteriorly the bladder, posteriorly the rectum and laterally the ureters and obturator nerves are the sole remaining tenants. At the completion of such a dissection, the surgeon may feel confident that local recurrence is unlikely and, in those patients in this series in whom subsequent operation or autopsy has been performed, the true pelvis has been found to be remarkably clear of growth and any metastases present to be strictly extra-pelvic.

(3) The extensive removal of the parametrium and paracolpos which is ideal from a cancer treatment point of view, is achieved at the risk of denervating the bladder. This has resulted in considerable bladder malfunction, stress incontinence, residual urine and loss of bladder sensation. This serious complication which is the great drawback of the extensive operation, is the main point on which it may justifiably be criticized. It is difficult to know how much a surgeon is right to prejudice the integrity of an adjacent structure when attacking a cancer though he should be prepared to accept the risk of injuring the innocent if he is thereby more certain of thoroughly eradicating the malignancy. When, therefore, the growth has extended down the vagina for a considerable distance, it is logical and proper to remove all this structure and all the paracolpos into which malignancy may have spread and no quarter must be asked or given since this is the very situation in which recurrence is to be expected. The ultimate greater safety of the patient considerably offsets the disadvantage of the urinary complications.

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ABDOMINAL DECOMPRESSION IN THE FIRST STAGE OF LABOUR

BY

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THE application of abdominal and lower thoracic decompression to parturients during actual contraction of the uterus has led to a substantial reduction in both the time and pain of the first stage of labour. Thus two-thirds to three-quarters of primigravidae had a first stage of under 5 hours duration, and all of them had relief of pain. The backache type of pain was always abolished, and much of the suprapubic pain was lessened. Forty per cent of women judged that the relief amounted to three-quarters or more of the pain.

The effect of decompression is to make the abdomen bulge forwards and outwards where the wall is muscular and able to stretch. Normally the shape of the uterus is that of the abdominal cavity with one long and two short axes. It is approximately ellipsoid. In so far as it is possible for the uterus to become more spherical its wall is able to shorten. When the epigastric region protrudes forwards during unaided contraction, the upper segment is changing its shape towards the spherical; but the uterus has to expend energy to overcome the resistance of the abdominal wall. If the abdominal wall is relaxed, this resistance is lower than when it is tense and, consequently, less uterine energy is dissipated. What is even more significant is the fact that, with adequate change of shape from ellipsoid to round, sufficient myometrial shortening and thickening of the upper segment can occur to facilitate the re-arrangement of muscular length which occurs normally in the two segments.

The decompression technique forces the upper abdomen and loins outwards, thus performing work on behalf of the uterus. In effect the abdominal cavity is caused to be rounder and, when a uterus in contraction is compressed from above into, or encouraged to become, something more spherical, the myometrium will shorten. On the contrary, the change in shape is resisted by a tense abdominal wall, and the result would be uterine contraction of the isometric variety. In the latter case shortening of the perimeter does not occur and contractions are ineffectual, resulting in the clinical entity known as inertia. The swelling of the abdomen is caused by decompression in the male as well as in the pregnant subject. It appears to be due to descent of the diaphragm: the pressure on its inferior surface is lower than that in the thorax, and the lower rib cage increases in girth just as in inspiration. The last movement is accompanied by an increase in the circumference of the abdomen at the level of the epigastric region and just below, because the muscles are fixed to the ribs.

The present investigation was undertaken when it was found unexpectedly that parturients experimentally curarized with scoline exhibited rapid dilatation of the cervical os. Regional analgesia and hypnotism were safer alternatives, but these methods were rejected. In a search late in 1954 for some means to control the tension of the abdominal musculature, reduction of the pressure on the abdomen below that of the atmosphere was contemplated. At the time it was thought that a pressure of one-fifth of an atmosphere might cause significant expansion of intestinal gas, reduce the weight of the atmosphere on the abdomen by about half-a-ton

and, finally, force down the diaphragmatic partition between thorax and abdomen. Personal experiments with the Kifa type of respirator indicated that low pressures were hard to bear, and the lowest limit attempted was half an atmosphere. This degree of partial vacuum proved to be unnecessary, because an increase in abdominal girth was conclusively established at two-thirds of a full atmosphere, i.e., 500 mm. Hg. The observations were made at an Air Force Station situated at 4,700 feet altitude and 650 mm. Hg atmospheric pressure. It was found subsequently that pressures of 100 mm. mercury below that of the surrounding atmosphere were sufficient to make the abdomen bulge. At present the usual range of decompression used in parturition is 40 to 50 mm. mercury below atmospheric, but almost the entire abdomen is included in the chamber in use.

The first chamber made for patients was in service in November, 1955. It consisted of a metal bucket with bonded rubber as a seal to fit the anterior aspect of the pregnant abdomen. This was followed by a transparent perspex dome with rubber seal. These chambers did not include the flanks which were compressed by atmospheric pressure relative to the anterior part of the abdomen protruding into the dome. In order to overcome this disadvantage, prototypes were constructed to contain the entire abdomen. At the end of 1957 a plastic bag with air-tight plastic zip was built to contain the body up to the part of the thorax just above the base of the breasts. A spacer made of steel rods was placed inside the bag over the abdomen and thorax with the patient sitting in a semi-reclining canvas-covered chair. This arrangement allowed decompression of the trunk except for the back, which is in contact with the canvas of the chair. The cases referred to in this paper were decompressed by this method.

The cases undertaken were all white women. In our service 2·4 per thousand spontaneous first labours had an unequivocal duration of under 5 hours for their first stage. Primigravidae only were used for the experimental series, and none with more than 2-fingers dilatation of the os. In 78 of the first 100, decompression was started at 0–1-finger dilatation and in 22 at 2-finger dilatation. Rectal examination was done by the same specialist throughout, and vaginal in addition where he was in doubt.

The patient sat down on the bag which had been laid open on the chair. The spacer or cage was placed in position with its lower rim fitting into the angle of the chair, and the 4-foot zip closed over the cage. The arms were left free and outside. As sealing over the chest is necessary, the suits varied in chest circumference from 28 to 38 inches with 2-inch gradations. Tubing from a 70 litre per minute suction pump was attached to a Y-piece sealed into the suit, the other limb of the Y-piece being connected with a pressure gauge. Various arrangements were made for control of the air entering and leaving the bag, but the patient was able to hold the connexion in her hand and close the vent with her thumb.

Decompression was carried out during contractions. The patient manipulated the valve, trying various pressures down to 50 mm. mercury (1 pound per square inch) below atmospheric, and endeavoured as soon as possible to become familiar with, and accustomed to, the effect on respiration. She was usually an apt pupil and co-operative, because she was soon aware of the relief of pain experienced during decompression. With a good seal the required pressure drop was attained within a fraction of a minute, and occasionally the parturient would reach as low as 100 mm. mercury and even more. There was a tendency to keep the basic pressure between contractions at 20 mm. rather than zero. The upper border of the suit fits around the chest just below the axillae, but the cage should reach to midway between the upper border of the breasts and the axillae. If the cage does not cover the epigastric region, the suit will make pressure there and impair expansion of the lower thorax and diaphragmatic descent.

It will be appreciated that air is sucked out of the bag. Around the lower extremities the suit clings tightly and the only partial vacuum present is that underneath the incompressible cage. The vacuum extends as a rule from the lower thorax to the vulva. The parturient sits in an unusually comfortable chair in a nearly

semi-reclining position, placing the long axis of the foetus practically vertical. At pressures below the usual 40 to 50 mm. mercury abdominal respiration is impaired and one resorts to upper costal breathing. This change in rhythm caused by immobilization of the diaphragm is not very unpleasant, but the relatively major changes in pressure demand a certain fortitude. To the patient the predominant feature is the relief of pain. The suit is easily opened to auscultate the foetal heart, and it is then that the woman realizes how unwelcome the pains are. She is comfortable in the chair, enjoys substantial relief, and she feels very little inclination to get up to walk about, lie on the bed, or even to wander off aimlessly to the toilet. There has been no accident with overlooking a late second stage. It is probable that some cases have been decompressed with a fully dilated os, particularly when this stage has been reached within 1, 2, or 3 hours. But clinical judgment is just as successful in determining the onset of the second stage during decompression as in orthodox deliveries. The patient is then removed to the labour ward for routine delivery. In no case has foetal distress been found to develop. Another unusual result seems to be late rupture of the membranes, and it is probable that intra-amniotic pressure is reduced during decompression.

Discussion of Rationale

As the pregnant uterus grows it assumes the shape of the abdominal cavity. This restriction together with uniform atmospheric pressure on the abdominal musculature makes the shape approximately ellipsoid. During contraction the uterus moves forward from the vertebral column becoming more spherical. Because the intra-uterine volume remains constant, such change from flat to round allows shortening of the myometrium. This is isotonic contraction, as opposed to isometric when there is no change of shape.

The last point must be considered further. First, there arises the question why the pregnant uterus tends to become round. The explanation offered at present is that the pregnant uterus is a viscus which is normally of spherical shape, and that it will return towards this shape whenever encompassed by insufficient force to flatten it. Reduction of the effect of the latter force occurs when myometrial tone increases and when abdominal muscle resistance is reduced. It seems reasonable to think of the uterus as being characteristically round because it is quite globular in the early weeks of pregnancy, it is round when firmly contracted post-partum, and a 16- to 18-weeks pregnant human uterus which we kept in labour *in vitro* maintained the shape of a pronounced sphere.

Under normal circumstances the relaxed viscus is compressed *in situ* into a sausage shape, but as soon as tension develops in its wall the stress will operate away from the centre outwards. Even if the restriction of the container is not overcome, the myometrium will act as does one's closed hand when opening it forcibly. The hand can work in the opposite direction by closing it firmly upon say a ball. If the contracting uterus is acting towards becoming rounder and bigger, the intra-amniotic pressure must drop. In so far as change of shape with resultant myometrial shortening occurs, the pressure is unlikely to drop much. However, a uterus round with excessive liquor amnii cannot change shape any further towards spherical: here there is true isometric contraction and a rise in intra-amniotic pressure must occur. The first of these cases has been substantiated experimentally (Heyns, 1959a).

It seems probable that the ideal contraction is the unhampered isotonic, because here at least the requisite thickening of the upper segment results from muscle-shortening following change of shape. The change of shape is mainly in the upper uterus, because during inspiration or the movement caused by decompression the increase in girth is very great at the level of the transpyloric plane, slight at umbilical level, and not appreciable at the transtubercular plane. The laying down of most of the contractile protein in the fundus is also likely to be of fundamental importance. It is obvious that when the uterus returns to the ellipsoid shape after a contraction, the wall must lengthen again; but it is also imperative that the upper segment should retain some of its shortening at the expense of the progressively stretching and thinning lower segment. Once the fundus is

thick and strong enough, muscle protein apart, to overcome the lower segment, the first stage changes proceed smoothly and rapidly.

It is difficult to escape the conclusion that the intrinsic pressure of the amniotic sac can rise only when the contraction is purely isometric. This would happen in polyhydramnios and severe oligohydramnios.

The two primary factors in the rationale are uterine and diaphragmatic action. The diaphragm moves in unison with the rib-cage and at present it is not possible to say which comes before the other and actually initiates the action. Two simple observations may be made at this stage. One is that the diaphragm as a partition between abdomen and thorax descends, as the pressure around the abdomen is reduced, in an attempt to equalize the pressures in the two chambers. There is a simultaneous increase in girth at the trans-pyloric plane. The descent of the diaphragm simulating a piston and the opening up of the lower rib-cage push the abdominal viscera forward into the new space provided by the bulging abdomen. The uterus is aided by the reduction of the supero-inferior axis and the increase in transverse and antero-posterior axes, for this telescopic or bunching effect not only allows it to assume a rounder shape but also forces it to become more spherical. The second observation follows from the first. Decrease in intra-abdominal pressure during decompression does not occur. Experiment shows that even where high decompression to −200 mm. Hg below atmospheric was undertaken with a view to exceeding diaphragmatic stretch, the pressure drop was negligible. In the region of the upper abdomen that lies within the lower costal cage, a pressure of −11 mm. Hg has been recorded in the peritoneal cavity during decompression.

The elementary structural and mechanical features of thorax, diaphragm, abdomen, pelvic girdle, and pelvic floor have been considered elsewhere (Heyns, 1959b).

Equipment

The equipment for the first stage of labour comprises four components. These are the chair, the pump, the plastic air-tight suit, and the incompressible spacer made of fibre glass.

The chair has been referred to: X-ray studies have shown that the long axis of the foetus is vertical with small variations when the mother sits in the chair. The pump required is of the roughing variety with capacity 70 litres per minute. It is inexpensive and has been more satisfactory than either larger or smaller suction pumps.

The suit is of laminated polyvinyl chloride with a gauge of 8/1000ths of an inch. A lower gauge tears readily and a thicker is not so pleasant to handle nor does it give such an efficient seal. A very thick nylon impregnated with polyvinyl chloride was used in the early stages, but is now thought of as very crude. As it is necessary to open the suit, there is a 4-foot long zip fastener running up the front. This is a plastic zip which is completely air-tight.

The perfection of the cage has been very troublesome, but it is hoped that one size with adjustable slides may serve practically all cases. The upper border of the cage has to come within an inch or so of the chest wall in order to prevent a process of the suit being forced downwards and on to the epigastrium. The same applies to the lower edge of the spacer, if decompression of the lower abdomen is desired, but less trouble has been experienced over the legs than on the chest. Most of the present series have been decompressed with a cage that does not reach high enough. This weakness was recognized early in 1958, but it was only a few weeks ago that a cage was designed suitable for the purpose. The material used was fibre glass and improved results are hoped for.

Case Reports

The following case reports have been selected to give a cross section of the results obtained.

Case 1

Mrs. E.S. Private patient. Age 25. Parity 0. Height 5 feet 6 inches. Delivered 6th January, 1959. Full term. Labour started 03.30. Contractions were irregular and lasted about 15 seconds occurring at 10-minute intervals. These gradually became stronger, of longer duration,

and at shorter intervals. At 09.00 there was a show. At 11.00 contractions occurred at 6-minute intervals, lasted 30–40 seconds, and were fairly strong.

Examination. Per rectum the cervix was found to be 1-finger dilated. Vertex presentation L.O.A. Head engaged.

11.45: Decompression. −50 mm. mercury for 60 seconds. Alleviation of pain was definitely noticed, particularly the lower back pain which had troubled her most of all before decompression. 11.55: −50 mm. mercury for 85 seconds. 12.00: −50 mm. mercury for 60 seconds. 12.03: −75 mm. mercury for 65 seconds.

Remarks. The patient attempted to endure a contraction without the aid of decompression, but after 15 seconds grabbed the valve and decompressed. There was instant relief of the backache. She said: "it relieved my pain almost entirely. I do not know what I should have done without the suit." She thinks the back pain is relieved entirely and the suprapubic pain almost so, comparing it with the "pre-suit" contractions.

12.08: −75 mm. mercury for 65 seconds. 12.11: −75 mm. mercury for 70 seconds. 12.15: −75 to −95 mm. mercury for 75 seconds. 12.19: −75 to −80 mm. mercury for 80 seconds. Again attempted a contraction without decompression, but after 10 seconds she had to decompress. 12.24: −75 to −95 mm. mercury for 70 seconds. 12.28: −75 to −100 mm. mercury for 80 seconds. 12.30: −50 mm. mercury for 30 seconds. 12.33: −75 to −100 mm. mercury for 65 seconds. 12.38: −75 to −100 mm. mercury for 70 seconds. 12.40 and 12.45: 2 contractions without decompression while listening to the foetal heart. 12.47: −75 mm. mercury for 60 seconds. 12.50: −50 mm. mercury for 55 seconds. Contractions are now stronger and more painful. Relief is about three-quarters. 12.54: −75 mm. mercury for 75 seconds. 12.59: −75 mm. mercury for 75 seconds. 13.03: −75 mm. mercury for 75 seconds. 13.06: taken out of suit. 13.15: per rectum cervix is practically fully dilated. 13.20: the patient wants to bear down and is transferred to the labour ward. 14.05: delivered of a 9 pounds 7 ounces male.

Remarks. Up to 13·03 there were 20 contractions and an additional 4 up to 13.20. There were, therefore, 24 contractions from the start of decompression up to full dilatation of the cervix. Up to 12.50 pain relief was complete in respect of the backache and about 90 per cent in respect of the lower abdominal pain.

On average this parturient was estimated to require another 200 contractions from the beginning of decompression to full dilatation. It is true that she may have had an unusually short first stage without decompression, but one has seen far too much of this to lead one to believe that decompression plays no part in facilitating labour. The striking observations regularly made on a parturient in the suit are the increase in frequency, in strength, and duration of the contractions. This labour proceeded from 1-finger to full dilatation in 24 contractions. This would in itself give a total of 0·12 of the expected pain, but because the pain relief was never less than 90 per cent, the true total suffered would be $0{\cdot}1 \times 0{\cdot}12$ or 1·2 per cent of the expected total.

Case 2

Mrs. S.v.V. No. 2369. Age 18. Parity 0. Expected date of delivery 11th May, 1958. Delivered 22nd May, 1958.

Contractions commenced 08.00 when they were weak and irregular. This lasted until noon when they became stronger. There was a show at 16.45.

Examination. The vertex is not engaged.

17.15: per rectum the cervix was 1-finger dilated and thick. The head was 1 inch above the ischial spines. Foetal heart rate 132 per minute. 17.20: decompression started. There is good sealing. The pressure used is −50/20 mm. mercury. 18.15: a dramatic change has occurred. Contractions now occur every 2 minutes with good relief of pain, and last 40 seconds. Per rectum the cervix is 4-fingers dilated with a rim all round. The head is below the ischial spines. 19.20: decompression stopped. 19.30: the membranes have ruptured. The foetal heart rate is 124 per minute. 20.10: the cervix is fully dilated. 20.29: delivery of a 7 pounds 3½ ounces baby.

Remarks. Excellent result. From a 1-finger dilated thick cervix to full dilatation took 2 hours 55 minutes. After 2-hours decompression the cervix dilated from 1 finger to 4 fingers. Excellent analgesia. Note the dramatic change in the character of labour at 18.15.

Case 3

Mrs. M.K. No. 4466M. Age 22. Parity 0. Expected date of delivery 12th April, 1958. Height 5 feet 1½ inches. Delivered 14th April, 1958.

Contractions commenced at 19.30, at first every 15 minutes, weak but gradually stronger. Now they come every 8 to 10 minutes.

Examination. The head is engaged. The foetal heart is satisfactory. The membranes are intact.

10.25: per rectum the cervix is 1-finger dilated and thick. 10.40: decompression commenced. There is a good seal. Immediately the contractions become more prolonged, stronger, and more frequent (every 3 minutes). Contractions later became very powerful. 12.20: the patient feels like bearing down. Decompression stopped. 12.25: per rectum the cervix is fully dilated. The patient is removed to the labour ward.

Remarks. Excellent result. From 1-finger dilatation, full dilatation was reached in 1 hour 40 minutes.

13.15: delivery of a 6 pounds 7 ounces baby. Second stage lasted 55 minutes. Good relief of pain.

Case 4

Mrs. E.v.W. No. 628N. Age 21. Parity 0. Expected date of delivery 8th August, 1958. Date of delivery 20th August, 1958.

There was a show at 05.00, soon after contractions had started. 12.15: contractions occur every 5 minutes.

Examination. This is a large foetus. The position is L.O.A. and the head is not engaged.

Per rectum the cervix is thick and 1-finger dilated. The head reaches to within 1½ inches of the ischial spines. The membranes are ruptured.

12.45: decompression started. 14.00: there is marked relief of pain. The patient takes the pressure down as low as −150 mm. mercury. 14.45: decompression stopped. There are very powerful contractions every 2 minutes. Per rectum the cervix is much thinner and 3-fingers dilated. 15.15: decompression continued. 16.00: decompression stopped. 16.20: the cervix is fully dilated. 16.35: delivery of a 9 pounds 2¼ ounces baby. The baby is well. The third stage is normal.

Remarks. A 1-finger dilated, thick cervix reached full dilatation in 3¾ hours. The analgesia was excellent. The decompression time was 2¾ hours. The result is regarded as excellent.

Case 5

Mrs. A.v.d.W. No. 3259N. Age 19. Parity 0. Expected date of delivery 22nd October, 1958. Height 5 feet 1½ inches. Date of delivery 26th September, 1958.

Contractions commenced at 23.00 on 25th September, 1958.

Examination. The vertex is engaged and in the L.O.T. position.

12.00: per rectum the cervix is 1-finger dilated and thick, and one-quarter effaced. 13.30: decompression started. The pressure used is −60/25 mm. mercury. The patient is quite relaxed and happy. Contractions occur every 5 minutes. She estimates that there is a three-quarters relief of pain, this relief being mainly of the backache. 15.15: decompression stopped. Contractions now occur every 1½ to 2 minutes. They are very powerful. Good analgesia is present. 15.30: the patient wishes to go back into the bag because her pain is "terrific". Pethidine 50 mg. is injected. 16.00: decompression continued. 16.15: the cervix is close to fully dilated. 16.35: on vaginal examination there is a thin rim of cervix. 17.05: the cervix is fully dilated. 17.15: delivery of a 6 pounds 4¾ ounces baby.

Remarks. This is a good result. From a 1-finger dilated, thick cervix to full dilatation took 3½ hours. The second stage lasted 10 minutes. The decompression time was 2¼ hours. The analgesia was excellent. The patient is enthusiastic about the method.

Case 6

Mrs. W.B. Age 16. Parity 0. Expected date of delivery 2nd October, 1958. Height 5 feet 6 inches. Weight 134 pounds. Delivered 20th September, 1958.

There have been vague, irregular contractions since 02.00. After admission they occurred every 10 minutes. There has been no show.

Examination. The head is engaged and the position L.O.A.

11.10: per rectum the cervix is ¼ inch thick, 1-finger dilated, and well applied to the foetal head. The head is felt ½ inch above the ischial spines. This patient is hardly in labour. Decompression will be tried to discover its effect. 11.40: decompression started. A slow drop in the pressure to −50/20 has been developed gradually over the past 40 minutes. There is three-quarters relief of both backache and suprapubic types of pain. 15.30: decompression stopped. Per rectum the cervix is over 4-fingers dilated. Labour has been stimulated to contractions occurring every 3 minutes. 15.40: decompression re-started. 16.00: decompression stopped. The patient is sent to the labour ward. 18.30: the os is fully dilated. The last rim of cervix has taken 3 hours to disappear, i.e., without decompression. 19.45: delivery of a 6 pounds 13½ ounces baby.

Remarks. This is regarded as a good result. From 1-finger dilatation to full has taken 6 hours 40 minutes. The decompression time was 4 hours 10 minutes. Labour was stimulated. It has happened on a number of occasions that decompression was stopped when there was only a rim of cervix left. It has been a specific observation that this last part of the cervix without decompression takes upwards of 3 hours to disappear. In another paper an explanation will be offered for this phenomenon.

Case 7

Mrs. S.F. No. 5191. Age 19. Parity 0. Expected date of delivery 14th November, 1958. Height 5 feet 2 inches. Delivered 12th November, 1958.

Contractions commenced at 15.00 on 11th November, 1958. There was a show at 22.45. 23.00: contractions occur every 3 minutes.

Examination. The head is not engaged but can be pushed into the pelvis. The position is L.O.A. Per rectum the cervix is 1-finger dilated and thick. This patient from our antenatal clinic came in requesting to have decompression. In other cases a patient is merely selected at our convenience.

23.15: decompression started. Relief is maximal at the low pressure of −20/5 mm. mercury. 00.45: decompression stopped. Contractions are powerful. Per rectum the cervix is 2-fingers dilated. The foetal heart is satisfactory. 01.00: decompression re-commenced. There is marked relief at −50/20 to −75/20 mm. mercury. The patient is very enthusiastic about decompression and the relief which she experiences. She claims that there is 100 per cent relief. 02.35: decompression is discontinued. The patient is very tired. She is given pethidine 100 mg. 05.40: the cervix is fully dilated. 06.30: delivery of a 6 pounds 12½ ounces baby.

Remarks. From a 1-finger dilated cervix to full took 6½ hours. The second stage lasted 50 minutes. The analgesia was excellent, varying from 75–100 per cent at various times. The decompression time was 3 hours 20 minutes.

Case 8

Mrs. H.N. No. 2547. Age 21. Parity 0. Expected date of delivery 6th June, 1958. Delivered 3rd June, 1958.

There has been intermittent backache and abdominal pain since 02.00. There was a show at 09.30.

Examination. The head is not engaged, is in the R.O.A. position, but it can be pushed into the pelvis.

11.55: short contractions occur at 7 to 8 minute intervals, and are not strong. Per rectum the cervix is thick, 1-finger dilated, and well applied to the head. The head reaches to within ¾ inches of the ischial spines. The membranes are intact. 13.15: contractions still occur at only 7 to 8 minute intervals, but they are slightly stronger. Rectal examination shows the cervix to be unchanged from what was found at 11.55. 13.30: decompression started. There is a good seal and this is a good, co-operative patient. A pressure of −45/20 mm. mercury is used. 13.45: contractions occur every 4½ to 5 minutes. There is fair relief of backache. 15.25: analgesia is excellent, three-quarters of the pain being relieved. The foetal heart is 146 per minute. 15.45: decompression stopped. Per rectum the cervix is 3-fingers dilated. 16.20: decompression resumed. The patient is very enthusiastic about decompression. 18.45: decompression stopped. Per rectum the cervix is slightly over 4-fingers dilated. The head is at the level of the ischial spines. 19.05: decompression re-started. There is wonderful relief. Contractions occur every 2 minutes and last 1 minute. 21.00: the patient wants to bear down. Decompression is stopped. Per rectum there is still a thin rim of cervix present. 21.30: the cervix is fully dilated. 22.00: the membranes are artificially ruptured. 22.20: delivery of a 7 pounds 11 ounces baby.

Remarks. This is a good result. From a 1-finger dilated thick cervix to full dilatation took 8 hours. Decompression time 6 hours 35 minutes. The patient was supremely happy in the bag, being in fact the best we had seen to date. She was decompressed virtually up to full dilatation.

TABLE I

Duration of Labour Stages from Start of Decompression. 100 Primigravidae

Time in Hours	Stage I Number	Stages I and II Number	Time in Minutes for the Groups Shown in Column 2		Remarks
			Stage II Average	Stage II Range	
1–	7	4	27	5–47	
2–	15 (5)	9	34	20–75	
3–	9 (3)	15	29	5–60	
4–	19 (3)	11	31	10–75	
5–	14 (1)	22	25	10–60	
6–	8	7	43	10–95	
7–	0	3			
8–	6	2	48	20–67	3 occipito-posterior.
9–10	6	5			
10+–20	12	15	46	20–80	5 occipito-posterior.
Over 20	4	5	33	19–50	4 occipito-posterior.
	100	98	35·0	5–95	

NOTES ON TABLE I

(1) 100 primigravidae are analyzed and (shown in brackets) 12 multiparae.
   (*a*) In 78 cases decompression was started at 0–1-finger dilatation.
   (*b*) In 22 cases decompression was started at 2-finger dilatation.
   (*c*) In no cases decompression was started at more than 2-finger dilatation.

(2) Sometimes decompression was stopped with a rim of cervix present. This frequently took a long time to disappear but the time up to unequivocal full dilatation was the one counted.

(3) There were two Caesarean sections not shown under Stage II.

Note on the 4 Stage I Failures (i.e., Over 20 Hours):

In 3 the pain relief was 70 per cent and in 1 50 per cent. The first had decompression for 10 hours and in some respects was not a failure. Two had decompression for just over 7 hours, one having contractions only during such treatment, and the other having been in labour for 36 hours previously. The fourth was decompression (for 5 hours) by request because inductions for postmaturity had failed.

TABLE II

Relief of Pain (100 Primiparae) for Individual Contractions

Relief Estimated by Patient	Primiparae	Duration of 1st Stage in the 9 Individuals Having Poor Relief of Pain	
		Hours	Minutes
Complete	2		
Very good	8		
Good	42		
Satisfactory	34	1	0
Fair	5	1	10
	91	2	40
		2	50
Poor	9	3	35
		4	0
		6	0
		8	50
		19	45
	100		

The ratio of total pain suffered to total pain relieved is reflected by the product of the duration fraction and the pain fraction.

The above patients were all white women. In our service 2·4 per thousand spontaneous first labours had an unequivocal duration of under 5 hours for their first stage.

An attempt to estimate the failure rate of the method must take into account (*a*) the short duration of the first stage, and (*b*) the relief of pain. The parturients are very much more interested in the latter and one has gained the impression that they tend to lose the sense of time. The tables raise the question whether all women did not benefit in one way or another, and careful consideration of individual disappointing results of either (*a*) or (*b*) above resulted in a firm conclusion that no case could be regarded as a failure.

CLASSIFICATION OF RESULTS

In view of the fact that relief of pain has to be correlated with the duration of the first stage, a classification of the achievement of decompression based on the interaction between quantity and quality suggests itself.

Four classes for duration were made:

Class 1 (D1) Up to 3 hours is something quite new and all that can be expected.

Class 2 (D2) 3+ to 5 hours is excellent.

Class 3 (D3) 5+ to 7 hours is still very good.

Class 4 (D4) Over 7 hours. This is in my opinion a failure.

Three classes for relief of pain are sufficient: RI excellent, RII good, RIII poor.

There would accordingly be 12 classes if all the possibilities are combined. D1 +RI, D1 +RII, D1 +RIII, D2 +RI, D2 +RII, D2 +RIII, D3 +RI could be classified as excellent. D3 +RII and D4 +RI would then be very good. D3 +RIII and D4 +RII are satisfactory and D4 +RIII is a failure.

The first 100 primiparae shown in Table I were classified and the consecutive percentages for the classes starting with D1 +RI and ending with D4 +RIII were 8, 9, 8, 15, 10, 4, 8, 4, 3, 20, 9, 2. On the basis of the previous paragraph the following achievement may be stated.

Excellent ..	62 per cent
Very good ..	24 per cent
Satisfactory ..	12 per cent
Failure	2 per cent
	100 per cent

Summary and Conclusions

A physical method of facilitating parturition has been used. For this purpose decompression of the abdomen and lower thorax to a level of 1 to 2 pounds per square inch below the pressure of the atmosphere has been used. The effect on the abdominal wall is to make it bulge forward greatly thus allowing the uterus to push forward (become more spherical) without being resisted by a tense abdominal wall.

Decompression stimulates labour even when early and while the contractions are still very weak. This is probably due to a reduction of the forces resisting the change of shape to spherical for, when contracting, a uterus always endeavours to change its flattened ellipsoid shape to round.

Thus spurious, tardy and inertia labours are altered to progressive by decompression, but as soon as the parturient is removed from the suit labour ceases or is markedly slowed down. The spectacular results are, however, obtained with the ideal irrevocable type of labour.

Results show that 98 per cent of parturients are helped. In 50 per cent the pain of labour and the amount of it is so trivial as to have become negligible.

When the two factors of duration of the first stage and pain relief are taken together, analysis shows the following achievement:

Excellent	..	62 per cent
Very good	..	24 per cent
Satisfactory	..	12 per cent
Failure ..	..	2 per cent
		100 per cent

The first stage is reduced to half or below that of the average time in over 70 per cent of primigravidae. There is substantial pain relief in over 90 per cent of labours.

Acknowledgments are due to Dr. Max Bloom, M.R.C.O.G., my Tutorial Assistant Obstetrician, who has been in charge of the clinical material used for decompression. Without his loyalty and devotion, and skill, it would have been impossible to bring the project to its present stage of development.

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THE HUMAN ELECTROHYSTEROGRAM: ELECTRICAL EVIDENCE FOR THE EXISTENCE OF PACEMAKER FUNCTION IN THE PARTURIENT UTERUS*

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STUDIES on pacemaker function in the uterus both in human and animals have been meagre. Ivy and Rudolph (1938), on the basis of observations made on the exposed uterus in operated primates, suggested that contraction waves originated at either or both cornua. In rabbits Reynolds (1939) observed contraction waves originating in the tubes, some of which were transmitted to the uterus resulting in contraction of its musculature. Steer (1954), studying the fast electrical pulses, felt that one of his records suggested propagation, but that evidence for pacemaker activity which was present in early labour disappeared as labour progressed. Alvarez and Caldeyro-Barcia (1954), utilizing intramuscular balloons, stated that a pacemaker exists at both cornua, although their published records in normal labour showed the contraction waves originating near the right cornu only.

In this report evidence for the existence of pacemaker function in the parturient uterus will be examined, on the basis of our studies on the electrohysterogram (Larks, Assali, Morton and Selle, 1957; Larks, 1957; Larks, Mackay and Morton, 1958; Larks and Dasgupta, 1958).

MATERIALS AND METHODS

Two hundred and ninety-three cases in labour have been studied, as well as an additional hundred cases in pregnancy. Briefly the technique of obtaining the electrohysterogram consists of rubbing the abdominal skin with ecg paste, which is then washed off. Small solder electrodes, 5 mm. in diameter, or nickel silver alloy disks, 1 cm. in diameter, have been used. For bipolar recording the electrodes are placed at 10 cm. longitudinal spacing on right and left sides of the uterus and are attached with strips of surgical tape. For unipolar recording, the procedure is similar, except that one electrode is placed on the uterus and the other placed as an indifferent electrode on the thigh. The right ankle is used as the common return.

Two types of instruments have been used. The first instrument chosen was a Leeds Northrup recording potentiometer. This instrument could amplify signals down to zero frequency and had adequate sensitivity in the millivolt range. It

* This research was supported, in part, by a grant-in-aid from the United States Public Health Service, RG 4462.

had the additional advantage of rejecting signals faster than one cycle per second. Thus interference from cardiac potentials, striated muscle and nerve, as well as power line hum, were rejected. A disadvantage of this system was the fact that it had a single channel only, so that information from one area only could be recorded. With this instrument the patient was provided with a hand switch so that she could signal the onset, duration and end of her labour pain.

The second instrument was an Offner 6 channel Dynograph. This recording system can also amplify slow signals down to zero frequency by means of a unique chopper system. The choppers break up the slowly varying uterine waveforms, which are then amplified at good efficiency at relatively higher frequencies and, finally, are reconverted by another chopper at the output end into an amplified replica of the original signal. The important advantage of multichannel recording is that several parts of the uterus may be studied simultaneously.

Results

The Waveforms of the Human Electrohysterogram

Figure 1 shows a representative electrical pattern obtained during the first stage of labour (Larks *et al.*, 1957). Time and amplitude calibrations were as shown. The period of each electrical complex corresponded to one uterine contraction, i.e., there was a one-to-one relationship between the electrical correlate and the uterine contraction. Letters have been assigned to portions of the waveform, the standard letter

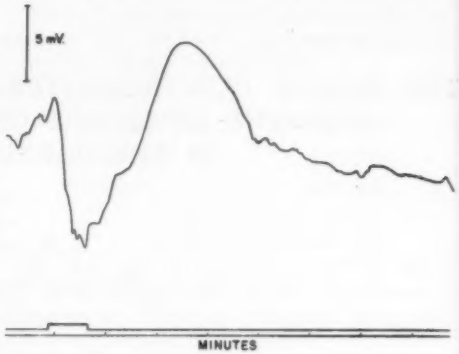

Fig. 1

One of the earliest clear examples of the human electrohysterogram. First stage of labour. The patient's pain signal is shown along the lower border.

U signifying the association with the uterus, while the subscripts are arbitrary and are not intended to have functional significance. Along the lower border of the figure is seen the signal from the patient's hand switch indicating the beginning, duration and end of the labour pain. The sharp and relatively unbroken U_{bc} deflection is of special interest. This was a bipolar recording with the Leeds and Northrup recording potentiometer.

Figure 2 shows a two-channel simultaneous record of the electrical activity of the right side (lower tracing) and left side (upper tracing) of the uterus. These tracings were recorded in a normally developing progressive labour (Larks and Dasgupta, 1958). The onset, duration and

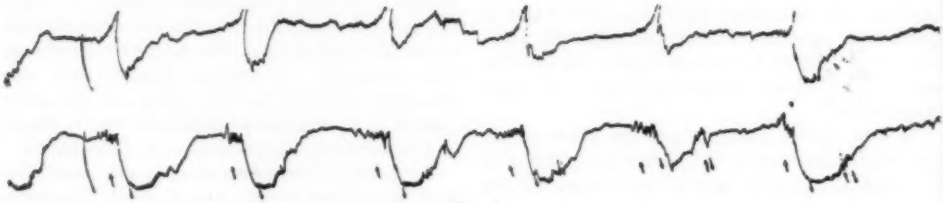

Fig. 2

Simultaneous recording of the electrical activity of the uterine right side (lower tracing) and left side (upper tracing) in normal labour. The arrow pointing up indicates the onset, and the arrow pointing down the end of the patient's pain sensation. Amplitude calibration of 5 millivolts is shown.

end of the patient's pain sensation are shown by the arrows. Amplitude calibrations of 5 mv. appear on the figure. It can be seen that on the right side (lower tracing) the pattern of the waveform was almost repetitive. Two frequency groups existed, one with the large amplitude waveform whose period was that of the uterine contraction, i.e., a slow event, measured in minutes. The second group consisted of higher frequency, smaller amplitude waves which appeared relatively early in uterine systole with a portion of the fast electrical activity appearing before the evident contractile events and before the subjective report of pain. The overall wave was dominantly monophasic.

The left side waveform (upper tracing) was similarly repetitive, but the morphology or wave shape was different. In this case a diphasic wave with an initial spike-like rise was observed with a sudden reversal and change of phase, and finally a slow recovery. The faster high frequency pulses were less evident. The time of onset of the high frequency pulses and also the time of onset of the sharp U_{be} deflection was greater for the left side waveforms. The first two events shown in Figure 2 are shown in amplified form in Figure 3. Interesting differences between the right and left side waveforms may be seen clearly.

Figure 4 illustrates a unipolar recording of

FIG. 3

Amplified portion of the previous figure, showing the first two contractions. Note the differences in waveform as between the right and left sides.

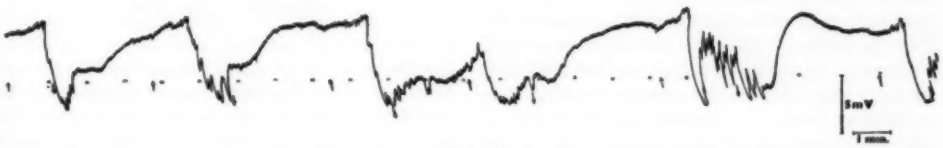

FIG. 4

A unipolar recording of the right side waveforms. The indifferent electrode is on the thigh.

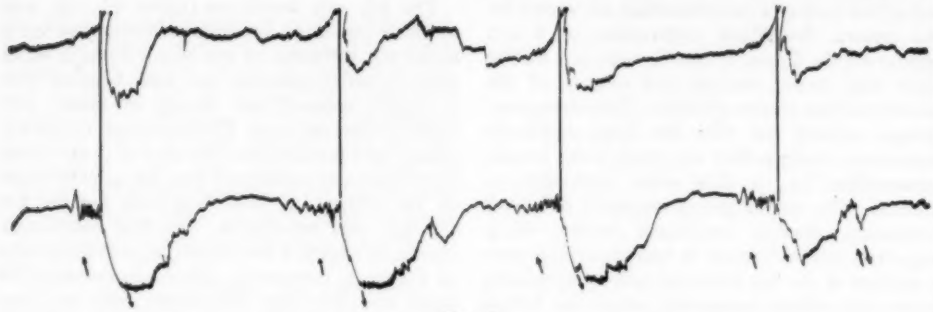

FIG. 5

The electrohysterogram of Figure 2, with timing tapes superimposed. The tapes have been placed such that their leading edges coincide temporally with the onset of the U_{bc} deflection on the right side. The U_{bc} deflection on the left side occurs at a later time.

the right side waveforms of the electrohysterogram in another patient in labour. In this instance, unipolar recording was used, with an indifferent electrode on the thigh and the exploring electrode on the right side of the uterus. The general outline of the waveform was similar to that reported earlier, using bipolar electrodes.

Figure 5 shows the waveforms of Figure 2, with timing tapes superimposed. The tapes have been placed so that their leading edges coincide temporally with the onset of the U_{bc} deflection from the right side of the uterus. It was observed that the left side U_{bc} deflection occurred at a later time than that of the right. Figure 6 shows a pair of electric waveforms from an earlier time in the patient of Figure 2. The later onset of the left side U_{bc} deflection was seen clearly.

FIG. 6

A pair of electrical waveforms from an earlier time in the patient of Figure 2. The later onset of the left side U_{bc} deflection is clearly seen.

Evidence from Studies on Pregnant Patients Not in Labour

In the course of studies of the electrical activity of the pregnant uterus prior to labour (Larks, Mackay and Morton, 1958), it was observed that there were periods of relatively little activity of any kind. At 25–30 weeks of pregnancy, there was neither marked electrical activity nor observable uterine contractions. Somewhat closer to term infrequent bursts of high frequency activity appeared though major propagated waves were absent. No contractions were associated with the high frequency bursts.

As the end of gestation approached, it was observed that isolated major complexes resembling those of labour appeared (Fig. 7), sometimes with obvious contractile response, sometimes without. As the subject went into labour, all three characteristics appeared, i.e.,

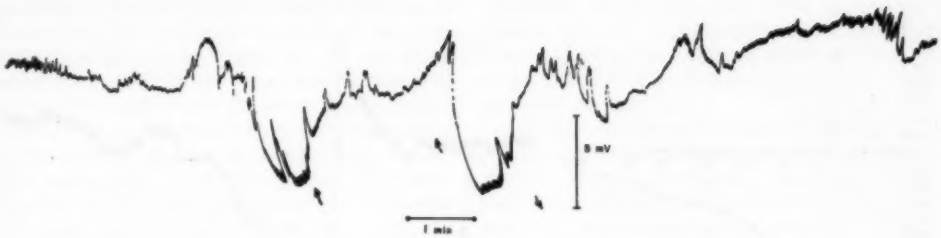

FIG. 7

In the tracing may be seen two of the isolated major U_{abcd} complexes which appeared in this instance at 38 weeks. By palpation, it appeared that the first complex was not accompanied by muscular response, whereas the second major complex was accompanied by an obvious generalized contraction. Examples of high frequency bursts may be seen to the left and to the right of the major complexes.

there were high frequency waves which are possibly associated with pacemaker function, the major U_{abcd} complexes associated with wave propagation and uterine contractions.

DISCUSSION

The repetitive character of the waveforms on each side of the uterus strongly suggests the existence of pacemaker areas. It is difficult to imagine the existence of a relatively simple and symmetrical waveform arising on the basis of uterine muscle contracting "in a mass". It seems much more likely that such a waveform is the correlate of a propagated uterine contraction arising in a definite focus.

Further evidence for a pacemaker and a propagated wave exists in the earlier onset of the sharp U_{bc} shift on the right side as compared with the left, suggesting that the focus is on the right side. The time difference between the onset of the right side U_{bc} deflection and that on the left is estimated to average 7·5 seconds for the first five complexes of Figure 2. (The sixth complex was recorded during a rectal examination and was therefore not considered to be recorded under physiological conditions.) This elapsed time may be taken as the time necessary for a wave to travel from a presumed focus on the right side to the left pair of electrodes. This value divided into the distance separating the electrode pairs (15 cm.) gives an estimated value of 2 cm./second for the velocity of the wave in the late first stage of labour.

The strongest evidence for the existence of a pacemaker arises from a consideration of the difference in the waveforms obtained from the two sides. One finds a monophasic waveform on the right side and a diphasic waveform on the left. What is the significance of this difference? Analysis of this problem has been made on the basis of physical and mathematical considerations. If a physico-mathematical model of a system involving radial spread of a dipolar wave of excitation is built up, and equations derived for the potential of an exploring electrode, as was done by Wilson and co-workers (1933) the result is a pair of complete elliptic integrals (of Legendre, see appendix). The waveform represented by these equations may be predicted and compared with electrohysterograms of the uterus. This has been done (Larks, 1957) and there is interesting agreement, as may be noted in Figure 8. From this agreement between theoretical considerations and experimental observation, it seems most reasonable to assume the existence of a pacemaker and propagated activity. The close parallelism argues that in the uterus, as in the physical model, excitation arises in a definite focus and spreads distally from it, i.e., there is propagation.

It should also be pointed out that a spike-like initial variation of a diphasic wave can be expected, theoretically, only at a distance from a

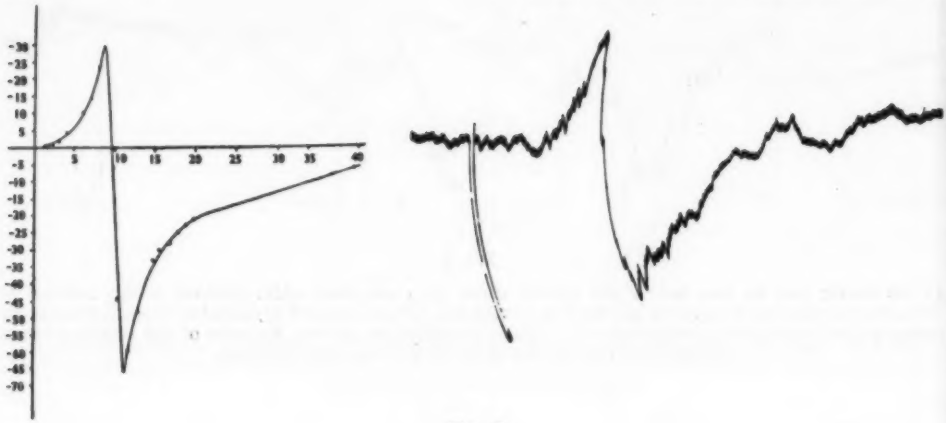

FIG. 8

Comparison of the predicted waveform based upon physico-mathematical considerations, shown here on the left half of the figure, with the experimentally observed electrohysterogram from the left side of the uterus. The electrohysterogram is shown here on the right half of the figure. There is good agreement.

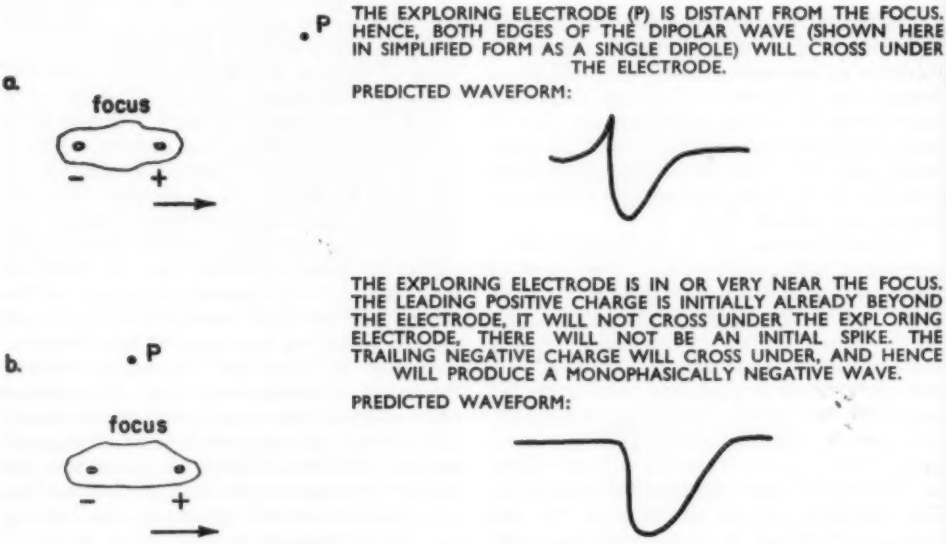
P
THE EXPLORING ELECTRODE (P) IS DISTANT FROM THE FOCUS. HENCE, BOTH EDGES OF THE DIPOLAR WAVE (SHOWN HERE IN SIMPLIFIED FORM AS A SINGLE DIPOLE) WILL CROSS UNDER THE ELECTRODE.
PREDICTED WAVEFORM:
a.
focus
THE EXPLORING ELECTRODE IS IN OR VERY NEAR THE FOCUS. THE LEADING POSITIVE CHARGE IS INITIALLY ALREADY BEYOND THE ELECTRODE, IT WILL NOT CROSS UNDER THE EXPLORING ELECTRODE, THERE WILL NOT BE AN INITIAL SPIKE. THE TRAILING NEGATIVE CHARGE WILL CROSS UNDER, AND HENCE WILL PRODUCE A MONOPHASICALLY NEGATIVE WAVE.
PREDICTED WAVEFORM:
b.
P
focus

FIG. 9

A dipolar wave, arising initially in the focus or pacemaker, is assumed to move out to the right as shown by the arrow. A schematic explanation to explain the genesis of the observed waveforms on a qualitative basis.

pacemaker, whereas in the vicinity of the focus a monophasic wave should be observed. If, as in the simplified case in Figure 9a, the recording point is distant from the focus, and the dipole is presumed to move past the exploring electrode, there will be contributions from both the leading positive charge and the trailing negative charge. The leading edge or positive charge will contribute the initial spike-like variation, the reversal will occur when the dipole is half-way under the electrode so that the contributions cancel and the slower recovery will correspond partly to the trailing off of the negative charge.

In Figure 9b, where the exploring electrode is assumed to be at or very near the focus, or region where the charge separation arises, it can be seen that the leading or positive charge will not cross under the exploring electrode and hence will not make a decisive contribution, thus no initial spike will result. The negative charge will cross, however, and will produce a monophasically negative wave.

Reference to Figure 2 shows a diphasic wave on the left side and a monophasic wave on the right side. This observation is in keeping with what might be expected (by the model) and supports the idea of one dominant pacemaker, apparently on the right side. Two pacemakers should give a considerably more irregular pattern, with either evidence of alternation, or of the late arrival of an electrical correlate from the opposite side.

Additional evidence of interest arises from a consideration of the high frequency components of the electrohysterogram, especially those observed in the right side wave-form. If, as seems probable, these components relate to specific pacemaker activity, their predominant appearance on the right side argues for localization of the dominant pacemaker on the right side. Supporting information exists in recent studies of specific pacemaker activity at the sino-auricular node of the heart (Van der Kooi, Durrer and Van Dam, 1956) which demonstrated high frequency discharges (Figure 10). In this figure, the electrical activity at the pacemaker of the heart is compared with the electrohysterogram of the right side of the uterus. There is considerable similarity.

The conception of a dominant pacemaker does not rule out the existence of a subordinate pacemaker. By analogy, the heart can be viewed as a two-pacemaker system in which one, the sino-auricular node, has become dominant,

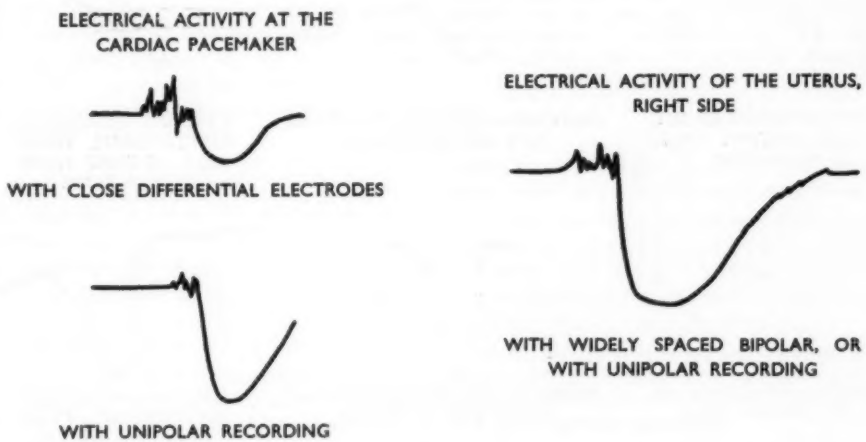
ELECTRICAL ACTIVITY AT THE CARDIAC PACEMAKER
WITH CLOSE DIFFERENTIAL ELECTRODES
WITH UNIPOLAR RECORDING
ELECTRICAL ACTIVITY OF THE UTERUS, RIGHT SIDE
WITH WIDELY SPACED BIPOLAR, OR WITH UNIPOLAR RECORDING

FIG. 10

Comparison of the electrical activity at the cardiac pacemaker with the electrohysterogram of the uterus, right side. There is interesting parallelism.

while the second, the auriculo-ventricular node, has become subordinate. There does exist, indeed, electrical evidence for some role for a subordinate pacemaker. Thus, in certain cases of uterine inertia, there has been observed the phenomenon of paired or coupled beats, in which pairs of contractions occurred at very short intervals followed by a long pause. This would fit in with the conception of a subordinate pacemaker which may sometimes be functional.

In discussing the observations made in mid-pregnancy, we began by noting that for repetitive, synchronous and generalized uterine contractions to occur, as in labour, three factors must be operating:

(1) The pacemaker must be functional, i.e., it must fire.

(2) Conduction over the uterine muscle must be possible.

(3) The muscle must be capable of response.

If the pacemaker alone fires, but conduction and contraction do not occur the observed electrical pickup should show fast, high frequency pulses. If now a wave of this excitation should spread, the major diphasic complex U_{abcd} would be recorded. Given the responsiveness of the muscle, a generalized contraction would result. It was suggested that these factors were inhibited in varying degrees during pregnancy and that, primarily, pacemaker activity was strongly inhibited. This idea was supported by the relative absence of the high frequency pulses in middle pregnancy, as well as by the fact that an adequate stimulus did occasionally cause a generalized contraction, thus showing conduction and response.

In late pregnancy, the rise in electrical activity is of the short duration pulse type, suggesting that increased pacemaker activity may be the earliest sign of the approaching end of gestation. More frequent appearance at

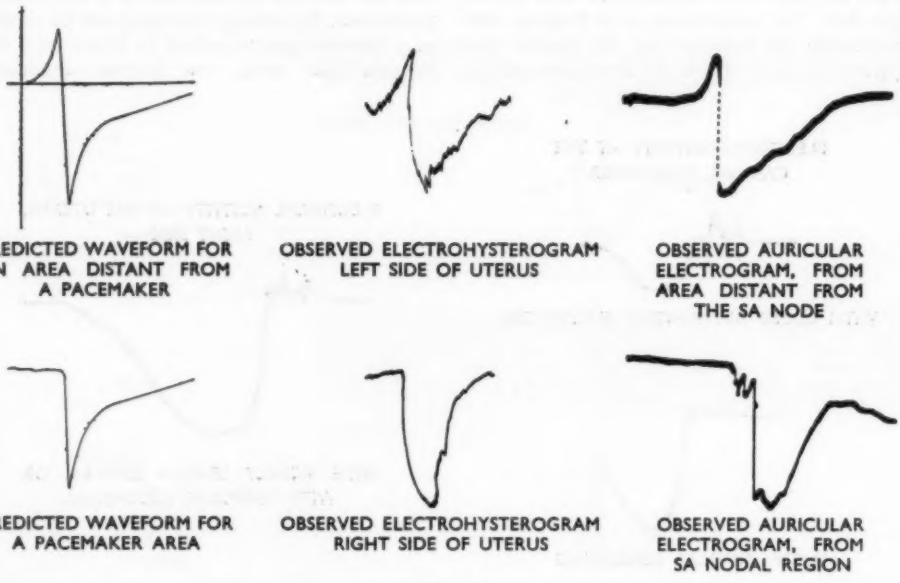
PREDICTED WAVEFORM FOR AN AREA DISTANT FROM A PACEMAKER
OBSERVED ELECTROHYSTEROGRAM LEFT SIDE OF UTERUS
OBSERVED AURICULAR ELECTROGRAM, FROM AREA DISTANT FROM THE SA NODE
PREDICTED WAVEFORM FOR A PACEMAKER AREA
OBSERVED ELECTROHYSTEROGRAM RIGHT SIDE OF UTERUS
OBSERVED AURICULAR ELECTROGRAM, FROM SA NODAL REGION

FIG. 11

The analogy between the cardiac right auricle and the uterus in labour. The parallelism is strong, suggesting that the uterus in labour behaves electrically like the cardiac right auricle.

37–38 weeks of major diphasic slow complexes would seem to indicate that propagation of the waves is beginning to take place more often. However, at this stage the major slow complexes are irregular and are often not associated with uterine contractions which may mean that the uterine muscle has not yet become fully responsive. Appearance of regular, synchronous diphasic complexes presumably indicates that the subject is going into labour or is in labour.

If there were no pacemakers, one would expect only a rise in irregular activity from random foci. If the uterus normally contracts "as a mass" there should be no evidence of wave motion or propagation, and no major complexes U_{abcd}. This is contrary to what has been observed. The evidence derived from electrical studies in pregnancy is consistent with the idea of pacemaker function and propagated electrical activity.

It may be instructive to compare the uterus with the cardiac right auricle. Electrograms from the latter organ may be compared with the electrohysterogram. This is done in Figure 11. Here the waveform in the vicinity of the sino-auricular node (Van der Kooi, Durrer and Van Dam, 1956) is compared with the EHG of the uterine right side, and a similar comparison is made of the auricular electrogram in areas removed from the pacemaker with the uterine left side electrohysterogram. The strong similarity lends support to the concept that the uterus is an auricle-like organ electrically, and suggests that the dominant pacemaker is on the right side.

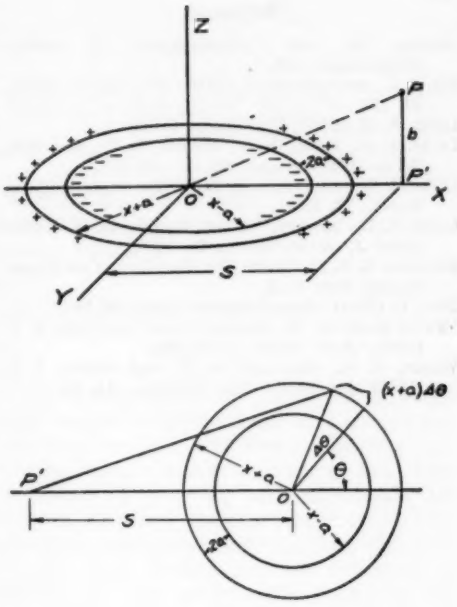

FIG. 12

The model as sketched by Wilson and co-workers, showing a dipolar wave of excitation spreading radially from a single pacemaker. The focus or origin is at point O, and the leading edge of the wave is shown as positively charged (outer circle) and the trailing edge as negative (inner circle). The exploring electrode or measuring point is at point P.

SUMMARY

(1) Electrical evidence for the existence of pacemaker function in the parturient uterus has been presented, and the implications discussed.

(2) The existence of the simple repetitive U_{abcd} waveform, in itself, indicates the existence of propagation arising in a definite focus.

(3) The existence of monophasic waveforms in a restricted area and diphasic waveforms elsewhere is evidence for the existence of a pacemaker.

(4) The later occurrence of the U_{bc} deflection on the left side as compared with the similar deflection on the right is evidence for a propagated wave and hence, for pacemaker function.

(5) On the basis of physico-mathematical models it is shown that the waveforms for the uterus can be predicted, and when the predicted and experimentally observed waveforms are compared there is good agreement.

(6) If the model is an approximation to reality, the uterus behaves as a single chambered organ in which excitation spreads radially from a single dominant pacemaker.

(7) The evidence derived from ante-partum studies supports the concept of pacemaker function.

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Appendix

On the basis of the physical model, the equation for the potential of an exploring electrode has been developed to be:

$$V_p = \frac{4\,c'\mu\,(x+a)}{\sqrt{(x+a+s)^2+b^2}} \int_0^{\frac{\pi}{2}} \frac{d\phi}{\sqrt{1-k_1^2 \sin^2 \phi}} -$$

$$\frac{4\,c'\mu\,(x+a)}{\sqrt{(x-a+s)^2+b^2}} \int_0^{\frac{\pi}{2}} \frac{d\phi}{\sqrt{1-k_2^2 \sin^2 \phi}}$$

THE MANAGEMENT OF THE CYTOLOGY TEST*

BY

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DESPITE the fact that in this century British workers had published papers on cytology there can be no gainsaying that Dr. George Papanicolaou of New York laid the foundation stone of the present-day cytological method of discovering cancer *before* operation, in his joint monograph with Dr. Traut in 1943. Cancer cells have been recognized microscopically for almost one hundred years. E. H. Shaw, L. S. Dudgeon and A. J. Wrigley have, in 1910, 1927 and 1932 respectively, published papers on the wet film method of examination of *fresh specimens* (though Dudgeon does mention one case of a smear from a tonsil which unexpectedly showed malignant cells and must have been taken as an out-patient test, for he says "otherwise the diagnosis would have been in doubt until after admission and valuable time would have been lost"). In most cases these workers were trying to hasten the pathology report of tissues obtained when the patient was already anaesthetized and a biopsy or a tumour immediately available. Dudgeon's descriptions of malignant cells are very much the same as Papanicolaou's, and between these two came W. C. McCarty who described the characters of malignant cells in 1934, but clinical application still did not follow.

In Edinburgh, at Professor R. J. Kellar's request, the method described by Papanicolaou was begun in 1949, in the University department of Obstetrics and Gynaecology, where all the gynaecological pathology for the South East Region of Scotland was also carried out. Between this time and Papanicolaou's monograph, many American papers had been published to help us, and particularly the Vincent Memorial Hospital's book (1950) with excellent illustrations and diagrams, the work of Dr. Ruth Graham and her colleagues in Boston. In 1951 we were able to present the results of our first thousand cases to the Royal Society of Medicine, and in June, 1955, our six years experience and results were presented with those from many other centres, at a Symposium in the Royal College of Obstetricians and Gynaecologists (Anderson, 1956).

There are now at least ten regions where gynaecological cytology is studied in this country; for study is the word rightly given to this work by Professor McKelvey of Minnesota. If the practice of cytology is merely one of reporting on smears, without the necessary subsequent study, then it may lead to the test falling into disrepute, or to insufficient numbers of cancers being found to encourage those doing it to continue and to improve. Cytology should never allow of the carefree interpretation of a test, the sending of a report, and, from that moment, the forgetting all about it, such as is possible for a biochemist carrying out a blood urea estimation. The unexpected positive cytology test always calls for sufficient interest by those reporting it, to pursue the clinician and pathologist, in order to confirm or refute the report. This means that it is inherent in the situation that the cytologist be given some hint

* From an Address to the Edinburgh Obstetrical Society, March, 1958.

of the clinician's suspicions, or otherwise, just as a pathologist carrying out an autopsy is entitled to a modicum of information about the events prior to his aid being sought. There are those clinicians who would be "scientists" and send specimens with no information, aiming to make the test "objective", but as in histopathology there may be many borderline lesions giving rise to differences of opinion, and the cytology test may not always be so clearly negative or positive that it can be compared with a leucocyte count, or a blood sedimentation rate reading. Cytologists with experience will naturally accept these specimens and give of their best, but only the patient suffers if the report is erroneous, and it is sometimes forgotten that the entire work is designed to further the solution of the patient's problems. Dr. Chandler Foot (1954) has argued this case for information being sent along with the specimen very cogently, but of course it is not a new request from pathologists, and cytology, in this respect, requires the same enlightened approach.

Why the Cytology Test Works

Initially Papanicolaou's test was made by aspiration of the secretions in the posterior fornix of the vagina, the aspirate being spread on a glass slide and immediately fixed in a solution of equal parts of alcohol and ether. It is believed that cancer cells desquamate or exfoliate more readily than benign cells. Many cytologists nowadays are inclined to use a contact or brushing method of obtaining cells, supposing this to be more fruitful, but use aspiration smears as well if they have time, or in particular cases.

The test is nothing more than very detailed pathological histology. Indeed all pathologists study cytology knowingly or unknowingly. They do this, however, in specimens made from shrunk tissues in paraffin blocks, whereas the wet film fixation used in modern cytology leaves the cells in a smear unshrunk and undistorted.

At the present day the proof of a tumour being malignant is generally accepted as a histological proof. The smear method is a cytology test and, useful as we choose to make it, it is only a test and not a proof, such as biopsy can be. However good we become at cytology, biopsy confirmation is always insisted on by those who have taken the trouble to learn the method and the time to examine a slide thoroughly. A study of the surface of an early squamous cancer of the cervix very quickly shows malignant cells already desquamated from the histological preparation, or ready to be brushed off by a wooden spatula. The surface of a benign area only shows flattened squames with pyknotic nuclei. Once we have realized and absorbed this, we can state three premises.

Firstly, malignant cells are there to be picked up and recognized. Secondly, they are more profuse in earlier lesions than in infected, necrotic disintegrating growths for which the smear method is of no accelerating value whatsoever. And thirdly, once we have accepted this, we have to acknowledge that the smallest cancer imaginable may provide malignant cells, lead to a positive smear report, and necessitate a tremendous task of serial sectioning of the confirming biopsy, before it can be demonstrated. The malignant cells are there, and if we wish we may try to obtain them and subsequently recognize them. It seems to me now, after nine years of this work, that the objections I heard earlier on against the claim that cytology is a reasonable and credible study have largely ceased. The objections now heard are more often that we do not know what to do about the early cancers which cytology helps to discover. Those who wish to treat so soon as they hear of a positive smear are failing to grasp the situation in two basic ways: first, that confirmation of the smear by biopsy must be the next step, and second, that the biopsy required to afford this confirmation, may, in the event, be sufficiently large to act as treatment.

Confirmation of the Unsuspected Positive Smear

The unsuspected positive smear comes from a cervix which a clinician regards as showing no obvious cancer when he sees it with the aid of a speculum. This definition must be kept simple. We learnt to call a cervix healthy, with intact epithelium, or eroded, by its appearance

alone. If there be suspicious associated symptoms such as intermenstrual bleeding, or post-coital bleeding, then our suspicions are aroused, but the appearance of the cervix remains the same. Confusion on this point leads some clinicians to describe a cervix as suspicious *in appearance*, because of its associated symptoms, which naturally leads to a higher rate of clinical suspicion, and a lower rate of cytological usefulness.

A higher rate of clinical suspicion is not necessarily a bad thing, provided it does not lead to an unnecessarily high rate of hospitalization and biopsy procedures requiring an anaesthetic. Many gynaecologists, particularly in America, having accepted that there may be cervical cancers which they cannot see, and in the absence of associated suspicious symptoms, employ a "quadrant biopsy" technique on out-patients, taking four "punch" biopsies from the junctional epithelium where these early growths appear to begin. Foote and Stewart (1948), however, demonstrated conclusively that some small and early lesions could still be missed even by multiple punch biopsy techniques, and Ayre (1948) submitted it was more logical to take an entire ring of tissue from the junctional epithelium. Nowadays, when we have realized that some growths may be so small as to be entirely removed by this ring biopsy procedure, it has become reasonable to remove a cone-shaped biopsy, with the cold knife, to include a large area of the portio as its base, and continuing to the internal os, for its apex. This is because a ring biopsy confirming an early cancer calls for meticulous examination by multiple blocks of the entire remaining cervix when received after hysterectomy, in the search for either further areas of early cancer left behind by the original ring, or for areas of invasion of a cancer appearing to be only pre-invasive in the ring. The newer practice of obtaining a cone may lead to the answer of both these questions, and if the answers are favourable, that is, that the knife has got beyond the lesion, and that there is no invasion, then the cone biopsy may turn out to be treatment as well, though naturally as careful a follow-up as for patients with visible cancers and more radical definitive treatment, is just as necessary.

But such a large biopsy as a cone cannot by any means be regarded as justifiable for every cervix which seems eroded or not completely healthy, and so we find cytology in its true place, telling us which cervices should be subjected to this method and which may be treated as benign. We may therefore outline our investigations of the benignancy or otherwise of a cervix in the following simple terms. *If cytology is not available* we continue with the traditional teaching of waiting for suspicious symptoms to be reported, or until we see a lesion on a cervix which we regard as a suspect lesion. With no suspicious symptoms and no suspect lesion we leave well alone, and our patients do not benefit from the diagnosis of earlier, smaller and invisible cancers. *With* suspicious symptoms but still no suspect lesion we probably carry out some type of biopsy technique which may or may not be adequate, for we cannot tell unless we take much larger biopsies for the very reason that we cannot see —in other words, a cone biopsy is necessary. With suspicious symptoms *and* a suspect lesion, then we remove the suspect (visible) lesion entirely for biopsy.

Where cytology is available:

(*a*) We may obtain positive reports from patients with no suspicious symptoms, and an apparently healthy cervix. (Most cytologists now have photographs of such cervices for demonstration purposes.) Here we must have a cone biopsy to afford us all possible tissue for examination.

(*b*) For a positive smear in a case with no suspicious symptoms but an *unhealthy* cervix short of harbouring a visible suspect area, the large cone biopsy is still required.

(*c*) For a positive smear from a case with no suspicious symptoms, but a visible suspect area it may be enough to remove that area alone, but more logical to employ a cone biopsy again, for the visible suspect area may be the wrong area.

(*d*) In the case of a positive smear associated with suspicious symptoms, and a visible suspect area, there is more likelihood of that area being the lesion from which the malignant cells have been harvested, but if

examination of this lesion did not confirm this, it could only be regarded as inadequate biopsy material. In the last set of circumstances, therefore, whether the biopsy is adequate or not will depend on the size of the visible lesion.

(*e*) Should there be a convincing malignant lesion, to the naked eye, *cytology is superfluous*, though academically interesting, for the area to be biopsied is not in doubt.

In short, if there is a cancer of the cervix not clinically obvious to the naked eye, it is a small and early cancer and probably "pre-invasive" or "*in situ*", and a single punch biopsy is quite inadequate to demonstrate it.

We have consistently based the value of our work on the harvest of cases in which the clinician *could see no cancer* and in gynaecological clinics this is 1 per cent or thereabouts. Howard Taylor, Jnr., has shown the fatuity of the "percentage accuracy" shibboleth in this work, for with only 1–2 per cent of cases to be found, we can boast of a 98 per cent accuracy for cytology by simply guessing all cases to be negative. Most clinicians using cytology have come to recognize that early cancer is just not visible, and in fact Sir Charles Read (1955) said, "As a result of all the investigations of cytology and cervical inspection I believe we have got to the stage where we hardly know whether the cervix is simple or malignant." Certainly if there is no clinical suspicion single punch biopsies can be grossly misleading, and if there is cytological suspicion they can be grossly inadequate. Where we are told of clinical suspicion but find no malignant cells we feel bound to advise that our report be ignored and that the clinician's customary biopsy habits be continued with, as if cytology had not been employed.

On the other hand, to bring into hospital for biopsy a high proportion of gynaecological outpatients on the grounds of suspect appearance of the cervix alone, is not only uneconomic but misses the point of cytology, implying as it does, that those who suspect a great number of cervices still believe that the naked eye can equal or improve on cytology and histology. The only justifiable cases for admission for biopsy are finally seen to be, firstly those with positive smears whatever the symptoms and appearance of the cervix; secondly those with a strongly suspicious appearance of the cervix even if the smear report is negative; and thirdly those with obvious clinical cancers. These three categories together should never reach the proportions of a tenth of the out-patients gynaecologists are asked to see.

Finally, in confirmation of the unsuspected positive smear it is essential that there should be a modicum of agreement about the early cancer, between the cytologist and the histopathologist. Not only must the clinician understand that his biopsy technique is all important, but also the pathologist must section the biopsy thoroughly and his mind must have accepted the possibility of finding smaller and smaller cancers, still invisible to the naked eye even after fixation and preparation in the laboratory. We have happily had no trouble in this direction for in Edinburgh we are fortunate in our gynaecological pathology being under the same roof as the cytology in the University department of Gynaecology. I would go so far as to say that our chief contribution to cytology in this country (for learning Dr. Papanicolaou's method requires only interest, aptitude and time) has been to study each unexpected positive case until a firm decision can be made by the clinician whose responsibility the patient must remain. We have of course heard murmurs of criticism (implying that we are both judge and jury) though nothing outright, nor in print, but we are unrepentant and in excellent company when we think of the late and revered Emil Novak, who although not a practising cytologist, fully realized the value of cytology in early and *in situ* cancers and knew how biopsies should be prepared, and what the early cancers looked like. Dr. Arthur Hertig also, although not practising cytology, has been, with Dr. Paul Younge, a leading contributor to the literature of the significance of the small early cervical cancers. But I have knowledge of five large teaching centres, both in this country and in America, where there has been incredulity on the part of the pathologist and consequent lack of interest and thorough study of biopsy material. Professor McKelvey of Minnesota has said that cytology should never be practised where there are not facilities

for proper study of each case and the lunch table gossip of cytologists includes many accounts of cases of early cancers which took weeks of search in almost inadequate biopsy material and weeks of persuasion of the pathologist (or even resort to a second opinion) before the cytologist's opinion was upheld.

The Edinburgh Results for Carcinoma of the Cervix

These may be quite simply presented, as follows, and refer to the number of cases discovered but not clinically suspected (Table I). *No clinically obvious cervical cancer is included in these figures.* To the end of 1957 our total

Table I

Clinically Unsuspected Cancers of Cervix Discovered by Cytological Test, 1949–1957

Total number of patients screened	19,464
Total number of malignant lesions	197 (1 per cent)
145 pre-invasive lesions	73 per cent
52 invasive lesions	27 per cent
Total number of gynaecological out-patients	16,276
Total number of malignant lesions	171 (1 per cent)
With the same proportion of pre-invasive and invasive lesions	
Average age of pre-invasive cases	37·8 years
Average age of invasive cases	50 years

Table II

Endometrial Cytology—False Negatives

1.	Menorrhagia, aet. 46	Curettage 13 days later—Adenocarcinoma.
2.	Post-menopausal bleeding	Hysterectomy for fibroids 2 weeks later without diagnostic curettage. Adenocarcinoma of endometrium=(missed clinically also).
3.	"Rectal" bleeding	Sent to surgeons. One month delay to discover that it was vaginal bleeding and post-menopausal. Adenocarcinoma in curettings 13 days after negative smear.
4.	Post-menopausal bleeding	Curettage 6 days later showed Adenocarcinoma of endometrium.

None of these cases suffered any delay from smear report being wrong.

Table III

Endometrial Cytology—False Positives

1.	Post-menopausal bleeding	Cervical polypi visible. Curettage within 10 days.
2.	Pain	Fibroids—Hysterectomy. No bleeding at all.
3 and 4.	Post-menopausal bleeding	Curettage 1 and 2 weeks later; no curettings obtained in either.

None of these had unnecessary treatment as a result of smear report.

Table IV

Endometrial Cytology—Correct Positives for Adenocarcinoma of Endometrium

1.	Post-menopausal bleeding	Unsuspected clinically. Clinical suspicions actually of *vulva* and patient given a date for admission "for investigation".
2 and 3.	Post-menopausal bleeding	Both given a date for hospital admission within 2 weeks of first attendance.
4.	Clinical suspicion of *cervix* and early admission arranged.	

In none of these did the correct smear report accelerate the diagnosis.

number of patients screened was 19,464 and a total of 21,627 smears have been examined. Over 5,000 of these have come from two groups outside hospital out-patient clinics—a Contraception Clinic and a General Practitioners' Group carrying out an investigation at our request, with help from the Research Funds of their own College (College of General Practitioners, 1958). The total number of cancers found is 197, 52 being early invasive neoplasms and 145 being pre-invasive (*in situ*) lesions—27 per cent and 73 per cent respectively. This is a discovery rate of just over 1 per cent, and the same rate was found for the 16,276 gynaecological out-patients, with the same ratio of invasive and pre-invasive cases. This is the rate of discovery we have consistently had since this work began, and it is on a par with most American hospital figures. The average age of the pre-invasive cases is 37·8 years, and of the invasive, 50 years. This is also comparable with American findings.

The Pre-Invasive Cancer Question

It will be seen that almost three-quarters of our score is made up of cases not yet invading into the cervical connective tissue. Entry of malignant surface epithelium into the mucous glands is not accepted as invasion. More than a quarter of our discoveries, however, are invasive lesions about which there would be little argument. (There might be some of course, for even general pathologists differ sometimes over quite visible and large tumours.) A pre-invasive cancer with much entry into the mucous glands, and the deep layers cut tangentially, may show circular nests or fingers, apparently invading (Fig. 1). As long as there is a circumscribed border, however, we still do not report such a picture as invasive, so we are pretty conservative. The earliest invasion we have found is illustrated (Fig. 2) and it is easily seen to be of a different pattern. In spite of this picture of early invasion, this patient was treated by amputation of cervix only, and this was followed by a successful pregnancy (spontaneous vaginal delivery). She is still well 5 years later, with negative cervical smears.

There has been a great deal of pother about this pre-invasive cancer, and so there should be, but a lot of it is unnecessary. We have written about it before and have little to add. It is not denied that we do not know that all pre-invasive neoplasms eventually invade, and if they do not all invade, which will and which will not; nor do we deny that spontaneous regression might occur, though I doubt it, for most records of such regression are associated with such multiple biopsy procedures that it is not surprising there is nothing left. This is not regression, it is removal.

Another pre-invasive cancer may enlighten those who cannot believe, and that is Paget's disease of the nipple. This has been an accepted malignant change in skin since Paget's first description in 1874. Evans (1956) says "that the changes seen in the epidermis are neoplastic and malignant is no longer in question". But sometimes the deeper mammary cancer was not observed until 10–20 years after the nipple lesion and controversy continues as to which lesion comes first. Of special interest to us, however, is the work of Dockerty and Harrington in 1951 at The Mayo Clinic, when by doing serial sections of the nipple in breasts removed for a deeper carcinoma, they showed Paget's lesion, when the nipple was normal to the naked eye. They called it Pre-clinical Paget's Disease, for the classical eczematous appearance was not in evidence. Paget's disease at the age of 84 has for long been a respectable member of the malignant neoplasm family, but pre-invasive malignant change of the cervix is the same age, having first been described by Sir John Williams in his Harveian lecture in 1886 (Williams, 1887). Some pathologists do not yet know it when they see it, and some report benign squamous metaplasia as malignant because they are hypnotized by the appearance it occasionally gives of invasion. The lesion on the cervix is undoubtedly pre-clinical in Dockerty's sense of appearing normal to the naked eye.

Since this cannot be a new lesion, why did it not appear as invasive cancer sufficiently often in the last 72 years to call for treatment? There are two answers to this at least. The first is that many cases did become invasive and have been recorded. Te Linde, Galvin and Jones (1952) gathered about 120 such cases a few years ago, and six alone have been published from

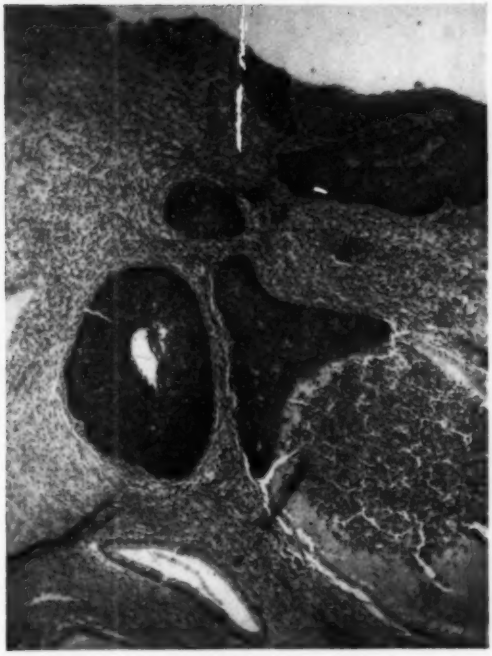

FIG. 1

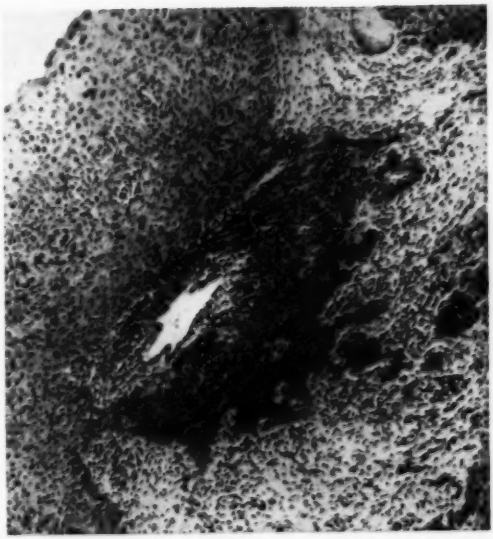

FIG. 2

Edinburgh (Anderson, 1950, 1953). But it was inherent in the older method of small chip biopsies that few patients with established cancer could be found with previous records of biopsies worth unearthing, even if available, for re-appraisal. The second answer is that cauterization of the cervix must have dealt unwittingly with many cases, as must amputation of the cervix in repair operations, and total hysterectomy for other reasons. Even rough handling with a gauze swab and certainly scraping with a curette can remove this superficial malignant epithelium.

No one, in point of fact, has ever advised that we ignore the pre-invasive lesion once discovered, and it certainly has dire potentialities. It should be emphasized again that there is an insoluble dilemma in attempting to assess these potentialities—the dilemma that for many cases of carcinoma *in situ, diagnosis is also treatment*. Cases with positive smears followed without biopsy confirmation are obviously unacceptable in attempting to discover the duration of life of cervical cancer. Cases with positive smears *after* biopsy showing carcinoma *in situ* may be followed by heroic and expert cytologists working in close harmony with gynaecologist and patient; but there must always be the lurking fear that there might have been invasion to be discovered had a larger specimen been available for biopsy, and that if so, the patient is still carrying it. Dr. Hertig (1957) again helps us by going so far as to point out that this problem is "scientifically incapable of proof". An interesting illustration of the difficulties in attempting it is that Kottmeier (1955) quoted 23 of 74 cases of cancer *in situ* which developed into invasive cancer, or 33 per cent. The following year in Chicago, having reviewed his histology in the interval, he quoted 15 of 31 cases becoming invasive, or 50 per cent; no treatment had been given following the original biopsy (Kottmeier, 1957). One of his cases developed invasive appearances *after an interval of 17½ years*. The only final diagnosis of carcinoma *in situ* is, of course, the careful examination of the total specimen. In some cases, residual "*in situ*" growth can be demonstrated, and occasionally early invasion, although not seen in the initial biopsy. Hertig (1957) has said that this is "the great 'joker' in this whole problem of carcinoma *in situ* that in order to prove it is truly *in situ* and not invasive cancer, you have to have the whole specimen". Whether or not there is any neoplastic epithelium left to discover in the whole specimen obviously depends on the size of the diagnostic biopsy originally taken.

Cancer of the Body of the Uterus

We are not good at this diagnosis cytologically. No cytologist appears to be as good with this as with cervical neoplasms. We are better than when we began but we find our labours largely unnecessary as the "unsuspected" case is much rarer. Cancer of the body of the uterus is never visible, so "clinical" suspicion is of quite a different nature in such cases. Also it occurs naturally at a later average age than cervical cancer and the specimen from curettage, so quickly arranged, is much superior as diagnostic material. Rare cases are known of course where a submucous fibroid has denied access to malignant endometrium by the curette, when a smear has been positive, and we are far from saying smears should not be taken or examined, but the tables illustrate details of twelve cases of this lesion which enlightened us about our own value to the clinician a couple of years ago. None of these patients was unnecessarily treated, nor neglected, whether we were right or wrong.

We believe it cannot be too strongly emphasized that investigations of this cancer must be kept strictly separate from those of cervical cancer, from the point of view of assessing cytological usefulness to the clinician.

In other genital sites we can record a positive smear from fluid ultimately collected in a cervical cap from a patient with two negative curettings for post-menopausal sero-sanguineous discharge. A primary tubal carcinoma was discovered at laparotomy in a patient too obese to allow of its clinical palpation. We did *not* report our positive smear with any suggested site for the malignant cells. Another positive smear for adenocarcinoma cells has just recently been encountered and this time with no clinical suspicion, for the case was one of

genital prolapse with no associated suggestive symptoms. A curettage revealed only the minutest threads of adenocarcinoma and laparotomy discovered a soft papillary cyst of one ovary, no larger than a billiard ball—also obscured to palpation by obesity. This harboured a papillary adenocarcinoma.

In none of these sites, however, have we such an accessible common cancer as uterine cervical cancer and it must be emphasized that it is here par excellence that cytology has proved of real help to patients and has, in Edinburgh, become as routine an examination as is the use of a speculum. Those who begin discussions about cytology by decrying the possibility of population screening of healthy and symptomless women are knocking down an Aunt Sally which in this country no cytologist has yet wished to set up. Miniature Mass Radiography must also have seemed impossible at one time, however, and I cannot help wondering, were cancer an infectious disease, if the public might take the matter right out of the hands of these critics, and who knows it may yet do so if it ever learns the survival rates for cancer.

It may be concluded with Bourne and Williams (1958) that pre-invasive cancer is not a killing disease and that we possibly have many years in which to detect it and treat it by total hysterectomy with prospects of 100 per cent cure. But it is further possible that conization or amputation of the cervix may be enough in younger patients desirous of a family.

In the future we may have help from biochemists or biophysicists in being clearer about what is and what is not cancer. It is unlikely, however, that we shall ever be without it for, as Smithers (1956) has pointed out, a final solution of this problem is impossible since it is part of the nature of complicated organisms that they cannot maintain their organization indefinitely. In other words it would be strange indeed if cancer did not exist. Smithers thought that the future lay with more efficient prevention or postponement of tissue disorganization. That is the case for the cytology test.

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PSEUDOMYXOMA PERITONEI

BY

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THE main characteristics of typical pseudomyxoma peritonei are well established, its usual relationship to ovarian tumours, rarely to mucoceles of the appendix, the widespread distribution of the gelatinous material throughout the peritoneal cavity, the tendency to recurrence, the unpredictable course to a fatal termination—a course sometimes rapid, sometimes very slow—and, even in frankly malignant cases, the long restriction of the lesions to the peritoneal cavity. Certain aspects of its aetiology and behaviour still call for discussion, in particular whether its origin is diversified or not, whether it is ever benign, and if not, what is its relation to the benign pseudomucinous cysts of the ovary, and finally the import of the massive peritoneal and parietal reaction so often present.

Originally pseudomyxoma peritonei was believed to be a primary peritoneal lesion. Virchow described one case as a myxomatous degeneration of the peritoneum or a chronic myxomatous peritonitis; another case as a gelatinous peritonitis. In 1884 Werth of Kiel established the ovarian origin of most cases. He reviewed the hitherto recorded descriptions, giving a detailed account of a personal case in which a laparotomy disclosed a ruptured ovarian cyst. Werth drew attention to the intense peritoneal reaction and the extensive round cell deposits in the subperitoneal tissues, a reaction which he pointed out was similar to the peritoneal response to foreign bodies. He considered that typical myxomatous deposits adherent to the peritoneum only develop with a lapse of some time after the spontaneous rupture of a cyst. This view indeed is still widely held and taught. It carries the tacit assumption that the intraperitoneal lesions are due to the escaped fluid rather than to explanted cells, one of the points calling for consideration.

Following Werth's paper many cases were recorded in the next few years. In 1891 Strassman discussed 30 cases and confirmed Werth's description, although neither from Werth's nor Strassman's accounts is it possible to be quite sure whether the primary ovarian lesions were malignant or not.

In 1885 Olshausen demonstrated that epithelial elements can sometimes be detected in the gelatinous masses.

In 1913 Thomas Wilson published an outstanding paper on the subject, with a chronological bibliography and a description of six personal cases. A spontaneous ruptured ovarian cyst was found in every one. One patient died of ileus nine days after a laparotomy. Of the remaining 5 patients, 1 died after 3 years, but 4 were alive and well for periods ranging from 2 to 9 years later. In the case in which death occurred after three years, epithelial cells were found in the omentum at the time of the initial operation. At the autopsy there was widespread infiltration and destruction of the abdominal muscles—the psoas, the iliacus, the obturator internus and the transversalis abdominis. In another case, still alive after 2 years, numerous masses were present in the subperitoneal tissues at the time of the operation.

Discussing Wilson's paper, Herbert Spencer described a case in which he had done three operations to remove the gelatinous masses. The patient was well three years later. At the last operation he had to "evacuate a cyst in the wall of the sigmoid colon", an interesting point in view of the possibility that the mucocele

of the appendix, which is sometimes an accompaniment of pseudomyxoma peritonei, may sometimes be a secondary rather than a primary lesion.

In 1930 Masson and Hamrick reviewed 30 cases of pseudomyxoma peritonei from the Mayo Clinic, occurring over a period of eighteen years out of a total of 7,800 oöphorectomies for all conditions. In these 30 cases 13 of the primary ovarian tumours were malignant, 17 were thought to be benign. Seven patients were known to have died after an interval ranging from one to eleven years, despite the fact that in 4 the primary tumour was considered histologically benign. In one of the fatal cases there was widespread destruction of the diaphragm. Masson and Hamrick were able to trace 12 of the survivors. In 5 of these the primary tumour was microscopically malignant; nevertheless these patients were still alive one, two, two, six, and five years respectively after the initial operation.

On the question whether pseudomyxoma peritonei has a single origin or not, Willis (1952) considers that pseudomyxoma peritonei "is not a single entity of uniform causation and prognosis. It is merely the result of profuse intraperitoneal extravasation of mucoid secretion of *any origin*" (my italics), adding that "this may come indeed from carcinomatous alimentary epithelium". Willis states that after a period of good health following surgical treatment, dormant cell residues may suddenly grow and speedily kill the patient.

The view that a diversity of ovarian lesions may lead to similar end conditions is supported in a stimulating recent paper by Rewell (1958), in which the homogeneity of many ovarian lesions, often considered to be separate entities, is stressed.

The diverse origin of pseudomyxoma peritonei is illustrated by the following cases, all of them malignant in differing sorts. They are described, not because they conform completely to the classical descriptions of pseudomyxoma peritonei, but because they may serve to elicit two points, one the diverse aetiology, the other that pseudomyxoma peritonei is a condition with a wide range, in which the classical case lies at one end of the scale.

Case 1. Pelvic Recurrence of a Corporeal Carcinoma

In 1949 a nulliparous woman, aged 52, had a total hysterectomy with removal of both ovaries for an adenocarcinoma of the corpus uteri. The growth seemed confined to the uterus. She remained well for 5 years and then reappeared with a cystic pelvic swelling reaching to the umbilicus. At laparotomy the typical appearances of pseudomyxoma peritonei were present. One gelatinous mass was dissected from the surface of the intestines. Microscopically the growth was a mucus-secreting carcinoma.

Three months later a swelling reappeared, this time firmly adherent to the left lower abdominal wall. The mass was excised together with the adherent transversalis muscle. The sections showed such an intense round celled reaction in the abdominal wall that the possibility of a sarcoma was considered.

Four months later further swellings appeared in the lower abdomen, these again infiltrating the abdominal wall. These were excised along with the adherent muscle together with three inches of adherent small intestine. By this time most of the muscles of the lower anterior abdominal wall were completely replaced by scar tissue. The patient died in 1958, 9 years after the hysterectomy, 4½ years after the first recognition of the pseudomyxomatous condition. No extraperitoneal metastases were found.

Features of the case were the prolonged survival time despite the malignant histological appearances, the restriction of the growth to the abdomen, the round celled infiltration of the abdominal wall, the destruction of the muscles, the secondary involvement of the intestines.

Case 2. A Malignant Teratoma of the Ovary

A nullipara, aged 20, was operated on for an ovarian tumour in December, 1949 and again in May, 1950. The initial diagnosis was a granulosa-cell tumour. She came under my care in June, 1950. At laparotomy the abdomen was found filled with pseudomyxomatous material, which lined the whole peritoneal cavity. As much as possible of this tissue was removed and on section found to be myxosarcomatous. Two months later a second laparotomy was necessary. More gelatinous masses were stripped from the parietal peritoneum and intestines. Histological examination of these showed the structure of a myxo-chondro-sarcoma.

Death occurred in September, 1950, about a year after the first appearance of a swelling. No extra-abdominal metastases were found.

A point of some importance is that the primary lesion was not an epithelial but a mesodermal tumour. The case closely resembles the malignant teratoma of the ovary reported by Dr. Harris and myself (Malpas and Harris, 1958).

Case 3. A Primary Adenocarcinoma of the Ovary

A nullipara, aged 56, developed an ovarian cyst in May, 1957. At laparotomy it appeared to be a typical unruptured pseudomucinous cyst of the left ovary. The

right ovary was normal. No other intraperitoneal lesion was found. The cyst was removed entire and without spill, together with the uterus and the right ovary. Histologically it proved to be a primary adenocarcinoma of the ovary.

The patient remained well for 9 months. She then developed an intestinal obstruction after some weeks of intermittent colic. At laparotomy the typical appearances of pseudomyxoma peritonei were seen, one of the masses obstructing the pelvic colon. The bulk of the peritoneal exudate was removed and the colon mobilized. She has remained fairly well since this operation, but there is still present an ill-defined lower abdominal tumour, firmly adherent to the lower abdominal wall and she has symptoms of a mild chronic intestinal obstruction. The ultimate prognosis is clearly hopeless.

These three cases, one a teratoma, one an adenocarcinoma of the uterus, one a primary ovarian adenocarcinoma, seem to support Willis's contention that pseudomyxoma peritonei has a diverse aetiology. Seeing that the primary lesion is so often an epithelial tumour it might be argued that the term "pseudomyxoma" is a misnomer, implying as it does that the lesion is always mesodermal in origin, and some of the confusion that still seems to surround the subject may be due to the traditional terminology.

In view of the fact that most and perhaps all cases of pseudomyxoma peritonei prove to be malignant in the long run, has the condition indeed any direct relationship to the common benign pseudomucinous cyst? That the two conditions are closely connected is a commonly held opinion, and of course the similarity between the contents of such cysts and the gelatinous exudates does indicate some relationship, but the weight of the evidence seems to support the view that the two conditions are not causally related.

In the first place cellular elements can usually be demonstrated in the peritoneal masses, remote from the primary tumour. Indeed, the failure to find them in every case may be due to the technical difficulties of their recognition. The fact, moreover, that the condition does recur entails the conclusion that cellular elements must be explanted, for otherwise the only possible origin of the myxomatous tissue would be the peritoneum itself, as Virchow originally stated.

In the second place, if the older reports of typical cases are studied, those cases on which the traditional teaching of a causal connexion between pseudomucinous cyst and pseudomyxoma peritonei is based, it is significant that the initial rupture of the primary cyst is always said to have been silent. But silent spontaneous rupture is indicative of invasive properties of the lining epithelium. Benign pseudomucinous cysts, on the other hand, almost always remain encapsulated and entire, no matter how large they grow, and their spontaneous rupture is very rare indeed. Certainly the escape of their contents into the peritoneal cavity, whether the result of tapping, or from a traumatic rupture, or from an accidental spill at operation, may determine a foreign-body type of peritoneal reaction, but this is rare and will not lead to pseudomyxoma peritonei. If this condition develops, then it must be inferred that the primary lesion was malignant. The common dictum that pseudomucinous cysts must be removed entire has little or no justification. Very often it leads to an unnecessarily long abdominal incision. In practice an accidental spill, often unavoidable, rarely if ever leads to any complications whatever, certainly not to pseudomyxomatous changes. When pseudomucinous cysts used to be treated by tapping, mucoid material must often have continued to be poured into the peritoneal cavity and collect there to excite a peritoneal reaction. Nowadays this sequence of events should be rare. Even if it has taken place, once the cyst has been removed and the patient has recovered from any peritoneal reaction, no pseudomyxomatous deposits will reform if the primary tumour was truly benign.

If pseudomyxoma peritonei is always a malignant condition, either epidermal or mesodermal, how can we account for the prolonged survival times of so many of the cases, even of those in which the primary lesion appears to be quite active? The restriction of the growth to the abdomen and abdominal wall and the rarity of remote metastases may suggest the answer. The intense peritoneal reaction around the explanted gelatinous plaques, a reaction often enough to destroy the parietes, closes all the surrounding tissue spaces and the lesions become as it were encapsuled.

There is little to be said about the treatment of pseudomyxoma peritonei. Operative treatment is necessary to establish the diagnosis and remove the primary cyst, but later should be reserved for the relief of symptoms, almost entirely the intestinal obstructive symptoms which so often develop towards the end of the disease. Most authorities consider the condition resistant to radiotherapy. Expectant treatment, combined perhaps with repeated tapping, is the proper course to adopt, for it is quite impossible to remove all the pseudomyxomatous material. Wilson (1913) made the interesting and sensible observation that the best way to deal with escaped pseudomucin is to irrigate the peritoneal cavity with normal saline solution, but of course such a procedure would only remove the exudate and not any explanted cells, and would be ineffective in a true case of pseudomyxoma peritonei.

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ERYTHROBLASTOSIS FOETALIS—A SURVEY OF THREE HUNDRED AND TWENTY-EIGHT CASES

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EXCHANGE transfusion has now become recognized as the treatment of choice in severe cases of erythroblastosis foetalis. There is, however, still a difference of opinion as to whether early induction of labour has a place in the treatment of this condition.

Early induction as a part of the treatment of erythroblastotic infants has been practised in the Brisbane Women's Hospital since 1949 with the intention of attempting to "salvage" severely affected infants who would otherwise have died *in utero* if permitted to go to full term.

Different workers use various methods of performing the operation of exchange transfusion. The method used here was described by one of us and has been followed in all cases (Dique, 1953).

It is our custom to use cold citrated blood from the refrigerator (6°–8° C.) which is of the same A.B.O. blood group as the baby, Rh (CDE) negative and not more than five days old. The transfusion is given slowly, i.e., at the rate of 100 ml. in and 100 ml. out per 15 minutes, and each infant is transfused with 100 ml. per pound of body weight plus another 100 ml. This has been shown (Dique, 1953) to give a 90 per cent exchange of blood in all cases and quantities of blood in excess of these amounts are without further benefit.

We have divided our 328 cases into three groups:

(1) 1st January, 1949 to 31st December, 1954—196 cases of which 183 were born in the Brisbane Women's Hospital and 13 were admitted after birth in other hospitals.

(2) 1st January, 1955 to 31st December, 1956—117 cases of which 103 were born in the Brisbane Women's Hospital and 14 were admitted after birth in other hospitals.

(3) Fifteen cases admitted to Brisbane Children's Hospital between 1st January, 1949 and 31st December, 1956, at varying times after birth for treatment of jaundice and/or anaemia due to erythroblastosis.

Group (2) were separated from Group (1) because during 1955 and 1956 some infants were treated with multiple exchange transfusions rather than single exchange as in Group (1); the reason being to remove excess circulating bilirubin which is harmful in itself and which is related more to hepatic insufficiency than to haemolysis.

Of the cases treated, 289 were given exchange transfusion. These transfusions were done by one or both of us together except in the cases of 6 transfusions which we supervised. One of us has always been associated with the treatment of every case in this series whether treated in the Brisbane Women's Hospital, or the Brisbane Children's Hospital.

Group (1). Between 1st January, 1949 and 31st December, 1954, a total of 196 erythroblastotic infants were treated in the Brisbane Women's Hospital, 183 were born in the hospital and 13 were admitted for treatment after

TABLE I

Year	Yearly Total Births and Deaths Excluding Cases Suffering from Erythroblastosis Foetalis						Yearly Total—Cases Suffering from Erythroblastosis Foetalis Admitted to Brisbane Women's Hospital						
							Live Births in Brisbane Women's				Born Before Arrival		
								Not Treated by Exchange Transfusion				Not Treated by Exchange Transfusion	
	Live Births in Brisbane Women's Hospital	Born Before Arrival	Neo-natal Deaths	Neo-natal Deaths Per 100 Live Births	Still-births	Still-births Per 100 Live Births	Treated by Exchange Transfusion	Treated by Simple Transfusion (All Lived)	No Treatment (Mild Cases all Lived)	Treatment Ineffectual (Died)	Treated by Exchange Transfusion	Treated by Simple Transfusion (All Lived)	Treatment Ineffectual (Severe Cases) (All Died)
1949	2,239	54	40	1·74	56	2·44	7	6	–	–	2	2	1
1950	2,661	64	56	2·06	53	1·94	21+1*	1	2	–	1	1	1
1951	2,947	93	56	1·84	62	2·04	21	1	1	–	1	–	–
1952	3,265	96	80	2·38	49	1·46	38	2	1	–	1	–	–
1953	3,334	105	72	2·09	79	2·30	37	–	–	–	–	–	1
1954	3,740	101	78	2·03	72	1·87	44	1	–	–	2	–	–
Total	18,186	513	382	2·04	371	1·98	168+1*	11	4	–	7	3	3
1955	4,024	67	68	1·66	60	1·47	40	1	–	1†	8	–	–
1956	4,004	75	80	1·96	67	1·64	60	1	–	–	6	–	–

* This baby was a mild case of erythroblastosis due to anti M and is not included in the analysis.
† Hydrops.

birth in other hospitals in the surrounding districts. A total of 23 infants died resulting in a total mortality of 11·73 per cent for the 196 infants treated. Of the 23 infants who died, 20 had been treated by exchange transfusion. The remaining 3 were born in other hospitals and were moribund on admission and not transfused. Treatment for these cases has therefore been regarded as ineffectual (Table I). The mortality therefore for those treated by exchange transfusion was 11·42 per cent. Of the other 20 who died, 8 (4·57 per cent of all cases treated by exchange transfusion) are regarded as unavoidable as the infants were too severely affected to have survived; the remaining 12 patients are deemed to have died of causes which are preventable. Seven of these infants died of kernicterus before the end of the fifth day of life—a second exchange transfusion might have prevented this. Two infants (1·14 per cent), had no antenatal supervision and were born at term severely affected—early induction might have prevented this. Three infants died as transfusion was being completed or shortly afterwards—their deaths have been attributed to heart failure which was possibly precipitated by too rapid a transfusion rate. A slower transfusion, or transfusion with small quantities of blood might have prevented this. These cases, and the 8 who died of unavoidable causes, are summarized with the fatal cases of Group (2) in Table IX.

The total of 11 unavoidable deaths, 8 treated by exchange and 3 in whom treatment was ineffectual, gives a total of 5·61 per cent unavoidable deaths for the series of 196 infants treated. This includes all cases, both mild and severe, whether born in hospital, or born before arrival and admitted subsequently from surrounding districts.

There were 31 stillbirths due to erythroblastosis foetalis during the six years under review (16·94 per 100 live erythroblastotic births in Brisbane Women's Hospital). Of these 17 infants (9·29 per 100 live births) died before the 36th week of gestation. These were regarded as unavoidable: the remaining 14 stillbirths (7·65 per 100 live births) occurred at intervals after the 36th week and may be regarded as possibly avoidable with antenatal supervision and early induction (Table II).

CONTROLS

During the six years under review a total of 18,186 infants were born in the Brisbane

TABLE II

	Percentage of Treated Cases Which Died in the Neonatal Period	Stillbirths Per 100 Live Births in Brisbane Women's Hospital	Stillbirths Per 100 Live Infants Treated
Total wastage ..	11·73	16·94	15·81
Unavoidable wastage	5·61	9·29	8·67
Avoidable wastage ..	6·12	7·65	7·14

Women's Hospital (excluding those suffering from erythroblastosis) and 513 were born before arrival and subsequently admitted, giving a total of 18,699 infants in all, which serve as controls. There were 382 deaths in the neonatal period (excluding those who died of erythroblastosis) and 371 stillbirths (excluding those with erythroblastosis). The neonatal death rate was therefore 2·04 per 100 total live births including those born before arrival, and the stillbirth rate 2·04 per 100 live births in Brisbane Women's Hospital (1·98 per 100 total live births) if those born before arrival are included.

The inclusion of those erythroblastotic infants born before arrival under the heading "live births" when working out the neonatal death rate has undoubtedly raised the mortality rate figures, because in this group there were 3 infants admitted in a total of 13 born before arrival in whom treatment was ineffectual.

It should be the aim of treatment to attempt to make the neonatal mortality rate and stillbirth rate due to erythroblastosis foetalis conform as closely as possible to figures for the control group. At the present time the best that can be hoped for is an approximation to the unavoidable wastage figures listed above.

ANALYSIS OF CAUSES OF MORTALITY

(Group 1, 1949–1954)

Mortality Rate in Respect of Maternal Anti Rh Antibody Titre

Of the 175 infants on whom exchange transfusions were performed the maternal anti Rh antibody titre was estimated within a fortnight of delivery in the majority of cases, while in a few it was estimated on the day of delivery or on the day following. The highest maternal anti Rh albumin agglutinating antibody titre recorded in each case has been taken to represent the titre at the time of delivery. The 175 infants have been grouped according to the highest maternal antibody titre recorded in each case and the mortality rate for each group calculated. The findings are shown in Table III.

It can be seen that, although the mortality rate rises with the maternal anti Rh antibody titre, there is a sudden dramatic rise in mortality when the titre reaches 1/128. The overall mortality rate for all infants whose mothers had attained an antibody titre of 1/64 or below was only 3·74 per cent whereas the overall mortality rate for all infants whose mothers had an antibody titre of 1/128 or above was 23·53 per cent. This is a very important finding in regard to treatment and demonstrates the undesirability of permitting pregnancy to go to term once a high maternal antibody titre has been reached. In fact, labour should be prematurely induced at the 36th week or after this directly it becomes

TABLE III

	Maternal Anti Rh Albumin Agglutinating Antibody Titre				
	1/16 and Below	1/32	1/64	1/128	1/256 and Above
Lived	41	32	30	22	30
Died	1	2	1	5	11
Mortality (per cent) ..	2·38	5·88	3·23	18·52	26·83
Overall mortality (per cent) ..		3·74		23·53	

TABLE IV

	Weight of Infant at Birth			
	5 pounds 8 ounces and Below	5 pounds 9 ounces to 6 pounds 8 ounces	6 pounds 9 ounces to 7 pounds 8 ounces	7 pounds 9 ounces and Above
Lived	21	46	49	39
Died	5	8	7	Nil
Mortality (per cent) ..	19·23	14·81	12·50	Nil
Overall mortality (per cent) ..	16·24		7·36	
	13·97			Nil
	11·42			

known that a high antibody titre is likely to be attained in order that the foetus be spared the harmful effects of the maternal antibodies at a time during pregnancy when they are known to be at their peak.

It must be clearly understood at this stage that the antibody tests must be carried out in the same laboratory, by the same technician, because skilled technicians frequently give results which differ slightly from those of other skilled workers. In the Brisbane Women's Hospital the tests have been carried out by the same technician (Miss N. Sylvester) using her own red blood cells. The results obtained are regularly one tube less than those obtained by the Red Cross Blood Transfusion Centre, Brisbane.

Mortality in Respect of Birth Weight

When the 175 infants are arranged according to weight at birth it can be shown that the mortality rate is inversely proportional to the birth weight. Nevertheless the mortality rate for infants of 5 pounds 8 ounces and below was less than for infants whose mothers had an antibody titre of 1/128 and above. This suggests that a low birth weight is in itself a less important cause of infant mortality than a high maternal anti Rh antibody titre.

The mortality rate of the 175 infants according to their weights at birth is given in Table IV.

Mortality in Respect of Prematurity

The mortality rate increases with prematurity as calculated from the mothers' last known menstrual period and is as shown in Table V. The findings are not so clear cut, however, as those obtained from the birth weight. The mortality rate for infants born 15 days and more prematurely is 13·86 per cent and for those born 14 days and less prematurely is 8·82 per cent.

TABLE V

	Days Premature				
	22 Days and More	21–15	14–8	7–1	Full Term
Lived	63	24	18	8	42
Died	9	5	1	1	4
Mortality (per cent)	12·5	17·24	5·21	4·11	8·69
Overall mortality (per cent) ..	13·86		8·82		

TABLE VI

		Haemoglobin Level		
		0–49 per cent (0·0 g.–7·35 g.)	50–79 per cent (7·5 g.–11·85 g.)	80 per cent (12 g.) and Above
Infants in whom cord-blood Hb. percentage was done	Lived	14	53	68
	Died	6	9	3
	Mortality (per cent) ..	30·0	14·51	4·22
Infants in whom peripheral blood Hb. percentage was done	Lived	—	6	14
	Died	2	—	—
	Total overall mortality (per cent) ..	36·36	13·23	3·52

Mortality Rate in Respect of Haemoglobin Level

The cord-blood haemoglobin level of 153 infants in whom exchange transfusion was performed had been estimated at the time the infants were delivered. In the remaining 22 infants the peripheral blood haemoglobin was estimated shortly after birth. All 175 infants have been subdivided into three groups depending upon whether the cord or peripheral blood haemoglobin was 0–49 per cent (0·0 g.–7·35 g.); 50–79 per cent (7·5 g.–11·85 g.); or 80 per cent (12 g.) and above and the mortality rate in each group is shown in Table VI.

It can be seen that, although the mortality rate rises as the cord-blood haemoglobin level falls the findings are not in agreement with those of Mollison and Cutbush (1949) in that here 70 per cent of infants with a cord haemoglobin percentage below 7·5 g. survived. Mollison and Cutbush claimed that very few infants survived when the cord haemoglobin level was below 7·5 g.

The mortality rates are biassed in the direction in which they lead if the numbers of infants in whom peripheral haemoglobin values only are available are added to those in the three cord haemoglobin groups and the total overall mortality then worked out.

It is interesting to observe whether the maternal anti Rh antibody titre has any effect upon the mortality rate of infants with varying levels of cord haemoglobin. Accordingly the infants have been grouped into three groups depending upon the cord haemoglobin levels:

Group 1 Hb. 0–49 per cent (0·0 g.–7·35 g.)
Group 2 Hb. 50–79 per cent (7·5 g.–11·85 g.)
Group 3 Hb. 80 per cent and above (12 g. and above).

Each group has then been subdivided into two subgroups depending upon whether the maternal anti Rh antibody titre was 1/128 and above or 1/64 and below, and the mortality rates for each subgroup are tabulated in Table VII.

It can be seen from this Table that a raised maternal anti Rh antibody titre adversely affects the chances of survival, for in each of the three groups the mortality rate of infants whose mothers had an antibody titre of 1/128 and above was greater than that of those infants whose mothers had an antibody titre of 1/64 and below. In addition to this the mortality rate of any subgroup of infants whose mothers had an antibody titre of 1/128 and above was greater than that of the preceding subgroup whose mothers had an antibody titre of 1/64 and below even though the cord haemoglobin level was much lower.

Infants in Subgroup 6 had a higher mortality rate than infants in Subgroup 3, although the latter group of infants had a lower cord haemoglobin percentage at birth.

Infants in Subgroup 4 had a higher mortality rate than infants in Subgroup 1, although the latter group had a lower haemoglobin percentage.

TABLE VII

Group	Hb. Level	Sub-Group Number	Maternal Anti Rh Antibody Titre	Mortality		Infants in Whom Peripheral Hb. Only was Available
1	0·0–49 per cent (0·0 g.–7·35 g.)	1	1/64 and below	Lived 4	20 per cent	—
				Died 1		—
		2	1/128 and above	Lived 10	33·33 per cent	—
				Died 5		2
2	50–79 per cent (7·5 g.–11·85 g.)	3	1/64 and below	Lived 30	3·23 per cent	5
				Died 1		—
		4	1/128 and above	Lived 23	25·8 per cent	1
				Died 8		—
3	80 per cent and above (12 g. and above)	5	1/64 and below	Lived 54	3·57 per cent	10
				Died 2		—
		6	1/128 and above	Lived 14	6·67 per cent	4
				Died 1		—

These findings suggest that a high infant mortality follows a high maternal anti Rh antibody titre rather than a low cord haemoglobin percentage at birth.

There were 22 infants in whom the cord haemoglobin was not available but in whom the peripheral haemoglobin had been estimated soon after birth. Their numbers have been omitted from the calculations in determining mortality but the infants in each subgroup are shown. It can be readily seen that the inclusion of these infants will only bias the findings in the direction in which they already lead.

There were 5 deaths (16·129 per cent) from kernicterus in Subgroup 4, and 2 deaths (3·57 per cent) from kernicterus in Subgroup 5. It can be seen that kernicterus is not an important cause of death in the very low haemoglobin group.

TABLE VIII

	Maternal Anti Rh Antibody Titre							
	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	1/2048
Stillborn	2	1	2	8	5	1	1	1
Stillborn, hydrops	1	–	2	–	1	1	–	5
Total	3	1	4	8	6	2	1	6
Percentage in each group ..	9·68	3·23	12·90	25·80	19·35	6·45	3·22	19·35
Percentage stillbirths in groups 1/64 and below and 1/128 and above		25·80				74·18		

Stillbirths

The 31 stillborn and/or stillborn hydropic infants have been grouped according to the highest maternal anti Rh antibody titre at the time the infant was stillborn. The number of infants in each group expressed as a percentage of all stillbirths was worked out and the results are shown in Table VIII.

It can be seen that 74·18 per cent of stillbirths occurred when the maternal anti Rh antibody

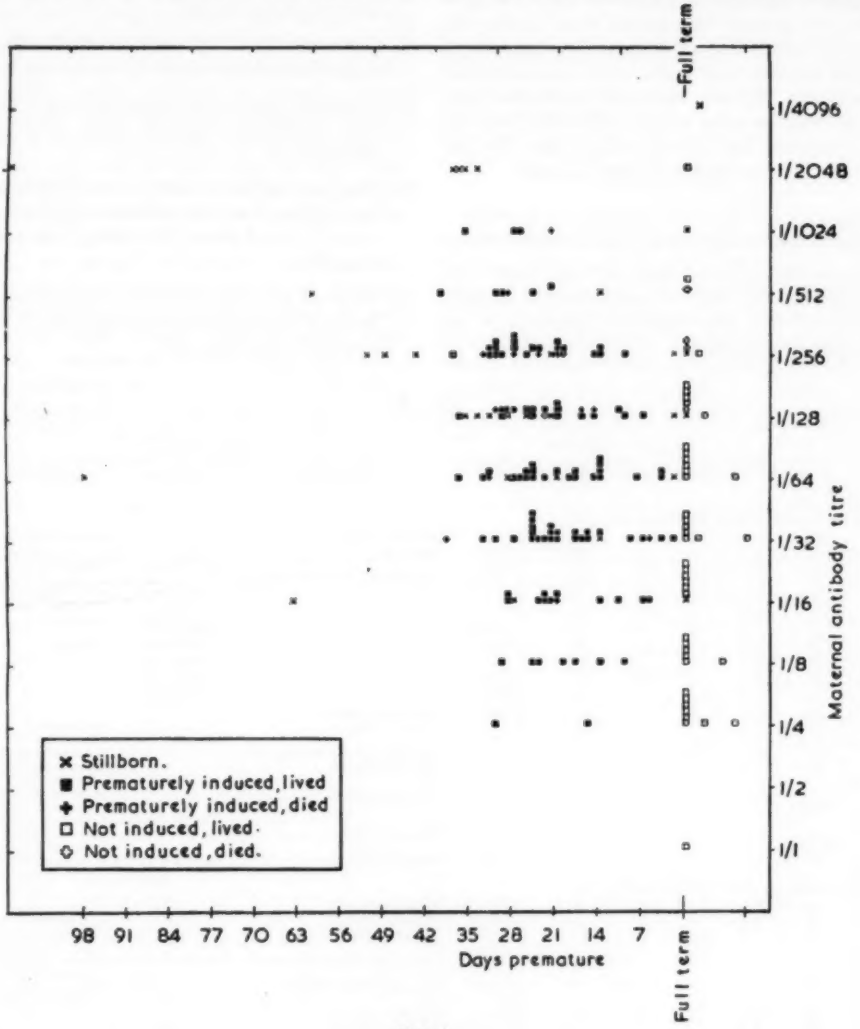

Fig. 1

Scattergraph of 175 infants who received exchange transfusion and 31 stillborn infants showing days of prematurity and highest maternal anti Rh antibody titre reached at time of delivery.

titre was 1/128 or above while a maternal anti Rh antibody titre of 1/64 and below resulted in only 25·80 per cent of all the stillbirths. The number of infants in each group is too small to be examined statistically. Nevertheless it appears that few infants died in the lower maternal antibody titre groups because at these levels the maternal antibodies are not unduly dangerous. It also appears that there were less stillbirths among the highest maternal antibody titre groups because most of the stillbirths likely to have occurred had already taken place by the time the highest level had been reached.

Analysis by Means of Scattergraphs

When the known facts of the cases are arranged in the form of scattergraphs a clear picture of the true state of affairs can be analyzed at a glance.

In Figure 1 the antibody titres and days of prematurity have been arranged as a scatter. It can be seen that:

(1) By far the greater number of stillbirths occurred when the maternal antibody titre was 1/128 or above.

(2) Some of the infants which were stillborn might have been saved by early induction.

(3) Neonatal death was associated more with a high maternal antibody titre than with prematurity.

(4) The proportion of fatal to non-fatal cases was higher when the maternal antibody titre was 1/128 and above than when it was lower than this.

(5) Most of the infants which were allowed to be born at term were associated with a "safe" maternal antibody titre.

Table IX

Patient	Cord Hb.%	Serum Protein	Weight		Maternal Anti-body Titre	Age at Death	Cause of Death		
			Pounds	Ounces			Unavoidable	Avoidable	Associated Diseases
Period 1st January, 1949 to 31st December, 1954:									
A	29	3·9	7	2	512	3 days	Severely affected	—	Intestinal haemorrhage
B	32	3·5	6	—	256	2 hours	Hydrops	—	—
C	87	4·7	6	3	64	6 days	—	Kernicterus	Pneumonia
D	39	—	6	12	128	3 hours	Severely affected, not supervised	—	—
E	55	5·1	5	10	128	3 hours	—	Heart failure	Atelectasis. Persistent occipito-posterior
G	84	5·9	7	4	128	4 hours	—	Heart failure	Atelectasis
Mo	30	5·3	6	13½	256	2 hours	—	Heart failure	—
L	50	5·5	5	—	256	5 days	—	Kernicterus	Melaena
M 1	54	5·5	6	1	128	4 days	—	Kernicterus	—
M 2	64	4·7	5	10	256	4 days	—	Kernicterus	—
M 3	70	3·6	5	4	256	5 days	—	Kernicterus	—
P	76	4·3	6	6	256	5 days	—	Kernicterus	—
R	68	—	4	12	128	12 hours	Precipitate breech	—	—
S	50	4·7	4	—	1,024	16 hours	Severely affected	—	Atelectasis
Se	82	4·3	7	5	16	5 days	—	Kernicterus	Haematemesis
R	30	4·3	5	6	32	29 hours	Severely affected. Hyperpyrexia	—	Pulmonary oedema
R 1	43	3·6	5	11	256	48 hours	Severely affected	—	Breech, gastric haemorrhage
W	34 (Periph)	—	7	6	256	24 hours	Severely affected	—	Subdural haemorrhage referred here after birth at term
Wo	48 (Periph)	—	5	9½	512	12 hours	Severely affected	—	Not supervised, gastric haemorrhage
C	77	5·5	6	12	32	13 hours	Severely affected	—	Poor general condition
Period 1st January, 1955 to 31st December, 1956:									
H	30	5·5	4	14	256	3 hours	Severely affected	—	—
H 1	55	4·3	4	11	256	4 hours	Severely affected	—	Precipitate birth
B	55	5·5	6	15	256	12 hours	Severely affected	—	Hyperpyrexia, respiratory obstruction
H	77	5·5	6	8	1,024	2 hours	Poor condition at birth	—	Absent diaphragm, tentorial tear
S	79	—	3	9½	256	4 hours	Poor condition at birth	—	Mongol. Right talipes. Absence both ears
F	26	5·9	4	10	256	12 hours	Severely affected	—	—
J	40	4·5	6	3	64	4 days	Severely affected	—	—
S	52	5·1	5	9	64	11 hours	Severely affected	—	Breech, contraction ring, shocked at birth

(6) Four cases might have had a better chance of survival if induced prematurely; as it happened they were born at term at a time when the maternal antibodies were very high.

The findings here suggest that in those cases where the maternal antibody titre is low (1/16 and below) labour should go to term; when it appears likely, however, that continuation of the pregnancy is likely to result in the foetus being exposed to the effects of a dangerously high maternal antibody titre labour should be induced early, i.e., as soon after the 36th week as possible providing the antibody titre (albumin agglutinating) is known to have reached a titre of 1/32 or above.

Due to minor variations in laboratory technique the "dangerous" level of maternal antibody titre should be determined in each laboratory which serves a labour ward. Alternatively, a number of antibody tests can be run off in parallel in two laboratories, one in which the "dangerous" level is known and one in which it has to be determined. The findings in the two laboratories can then be compared.

TABLE X

	Percentage of Treated Cases Which Died in the Neonatal Period	Stillbirths Per 100 Live Births in Brisbane Women's Hospital	Stillbirths Per 100 Live Infants Treated
Total wastage ..	7·89	7·77	6·84
Unavoidable wastage	7·89	7·77	6·84
Avoidable wastage ..	—	—	—

PART TWO

Between 1st January, 1955 and 31st December, 1956, a total of 117 infants were treated in the Brisbane Women's Hospital. Of these 103 were born in the hospital and 14 were born before arrival and were subsequently admitted from surrounding hospitals for treatment. The 14 infants admitted from surrounding hospitals all survived following exchange transfusion; 3 of them had been treated by exchange transfusion prior to admission and were given a second exchange transfusion after admission.

TABLE XI

Infants Treated by Exchange Transfusion Whether Born in Brisbane Women's Hospital or Admitted Later

		Treated 1.1.49–31.12.54		Treated 1955 and 1956			
				All Cases Treated		Cases Born in Brisbane Women's Hospital Only	
		No. of Infants	Percentage	No. of Infants	Percentage	No. of Infants	Percentage
Maternal Antibody titre	1/64 and below	107	61·1	61	53·5	54	54
	1/128 and above	68	38·9	53	46·5	46	46
Days premature	22 days and over	72	41·1	36	31·6	35	35
	15–21 days	29	16·6	30	26·3	27	27
	0–14 days	74	42·3	48	42·1	38	38
Birth Weight	5 pounds 8 ounces and under ..	26	14·9	16	14·0	13	13
	5 pounds 9 ounces–6 pounds 8 ounces	54	30·9	25	21·9	25	25
	6 pounds 9 ounces–7 pounds 8 ounces	56	32·0	40	35·1	36	36
	7 pounds 9 ounces and over	39	22·3	33	28·9	26	26
First Hb. estimation made	0–49 per cent	22	12·6	9	7·9	9	9
	50–79 per cent	68	38·9	33	28·9	29	29
	80 per cent and over	85	48·6	72	63·2	62	62

There were 8 stillbirths of which 7 were hydropic and 1 very premature non-hydropic infant. These 8 stillbirths are regarded as unavoidable as all of them occurred prior to twenty-eight days from the expected date of confinement.

There were 8 neonatal deaths all of which have been regarded as unavoidable because of their poor general condition and associated diseases. They are listed in Table IX.

The wastage figures for the cases treated during 1955 and 1956 are shown in Table X.

As these mortality rate figures are much lower than those found for the previous years it is important to determine whether an unusually healthy group of infants was treated during 1955 and 1956. In order to do this all infants born between 1st January, 1949 and 31st December, 1954, have been compared with those treated between 1st January, 1955 and 31st December, 1956, the criteria for determining severity being: (1) maternal anti Rh antibody titre, (2) birth weight and (3) days of prematurity. Table XI indicates the manner in which the two groups compare.

It can be seen that the infants treated in 1955 and 1956 did not differ significantly from those treated during the period 1st January, 1949 to 31st December, 1954. A greater percentage of infants treated during 1955 and 1956 were born of mothers in whom the anti Rh antibody titre was above 1/128 than in the preceding years. On the other hand they tended to be slightly, though not significantly heavier and to have slightly higher haemoglobin values, though the degree of prematurity was about the same. It must, therefore, be assumed that the further reduction in mortality is due to the manner in which these infants were treated. Multiple transfusions to reduce the serum bilirubin level have undoubtedly prevented kernicterus or reversed its effects when it developed. Slow massive transfusions have prevented heart failure and watchfulness on the part of obstetricians has resulted in infants being prematurely induced who might have been stillborn or born dangerously ill at term.

As regards multiple transfusions, a serum bilirubin level of 15 mg. per cent is taken as an indication for repeating the exchange transfusion as serum bilirubin levels above this are dangerous (Billing *et al.*, 1954; Hsia *et al.*, 1952, 1953).

As premature induction of labour has been practised many times during the last eight years it is necessary to determine what effect early induction has had on the various weight groups of the infants treated. In order to do this a study was made of 500 normal living consecutively born infants who serve as controls. The numbers of infants in each weight group and their percentages are given in Table XII. For comparison the percentage of treated infants in the various age groups taken from Table XI is again presented in Table XII for ready reference.

It can be seen that a significantly large number of infants have been born in the lighter weight groups during all the years while the number of infants in the heaviest weight group has been proportionately reduced.

Survival Rates

Until now the discussion has dealt with the analysis of stillbirths in the Brisbane Women's Hospital separately from infants born alive,

Table XII

Birth Weight	500 Normal Infants		Percentage of Infants Treated in Each Weight Group (Table IX)		
	Number in Each Weight Group	Percentage	All Cases 1949–54	All Cases 1955–56	Cases Born Brisbane Women's Hospital 1955–56
5 pounds 8 ounces and under	49	9·8	14·9	14·0	13
5 pounds 9 ounces–6 pounds 8 ounces ..	60	12·0	30·9	21·9	25
6 pounds 9 ounces–7 pounds 8 ounces ..	125	25·0	32·0	35·1	36
7 pounds 9 ounces and over	266	53·0	22·3	28·9	26

whether born in the Brisbane Women's Hospital or admitted subsequent to being born. Survival rates should, however, be taken as a percentage of all foetuses presenting for treatment prior to birth. There are enough cases treated during each year for the analysis to be done on a yearly basis and it is interesting to observe the effects produced by early induction on total survival rates during successive years.

The numbers of cases presenting for treatment (inclusive of stillbirths) have accordingly been grouped under their respective years, the total which were prematurely induced and treated by means of exchange transfusion determined and the percentage that these formed of the total number of cases worked out for each year. Similarly, the percentage of all cases presenting for treatment who survived or who died in the neonatal period or were stillborn have been worked out and the findings are given below. Of necessity, the analysis has had to include separately (*a*) all cases treated in Brisbane Women's Hospital, whether stillborn, live born or admitted subsequent to birth and (*b*) all cases live born and stillborn in the Brisbane Women's Hospital only (Table XIII).

Exchange transfusion was carried out on some of the cases which were not induced, and was, therefore, responsible for increasing the survival of this group of cases.

When the percentage of infants surviving, prematurely induced, stillborn and those who died prematurely in the two tables above is expressed graphically for successive years, a most interesting finding results. It can be seen (Figs. 2 and 3) that the line for surviving infants follows that of the line for the percentage of prematurely induced infants, rising and falling with the percentage of prematurely induced infants, each year, with a fair degree of parallelism.

TABLE XIII

		1949	1950	1951	1952	1953	1954	1955	1956
(*a*) All Cases Treated in Brisbane Women's Hospital Including Those Born Before Arrival:									
Total cases presenting for treatment including stillbirths and those born before arrival		20	31	27	46	47	56	55	70
Stillbirths	Total	2	4	3	4	9	9	5	3
	Percentage	10·0	12·9	11·1	8·7	19·1	16·1	9·1	4·3
Neonatal deaths	Total	5	3	2	3	6	4	2	7
	Percentage	25·0	9·7	7·4	6·5	12·8	7·1	3·6	10·0
Prematurely induced and treated by exchange transfusion	Total	5	12	14	30	26	36	35	50
	Percentage	25·0	38·7	51·8	65·2	55·3	64·3	63·6	71·4
Survivors	Total	13	24	22	39	32	43	48	60
	Percentage	65·0	77·4	81·5	84·8	68·1	76·8	87·3	85·7
		1949	1950	1951	1952	1953	1954	1955	1956
(*b*) All Cases Born in Brisbane Women's Hospital Only:									
Total cases presenting for treatment including stillbirths		15	28	26	45	46	54	47	64
Stillbirths	Total	2	4	3	4	9	9	5	3
	Percentage	13·3	14·3	11·5	8·9	19·6	16·7	10·6	4·7
Neonatal deaths	Total	3	2	2	3	5	4	2	7
	Percentage	20·0	7·1	7·7	6·7	10·9	7·4	4·3	10·9
Cases induced prematurely and treated by exchange transfusion	Total	5	12	14	30	26	36	35	48
	Percentage	33·3	42·9	53·8	66·7	56·5	66·7	74·7	75·0
Survivals	Total	10	22	21	38	32	41	40	54
	Percentage	66·7	78·6	80·8	84·4	69·5	75·9	85·1	84·4

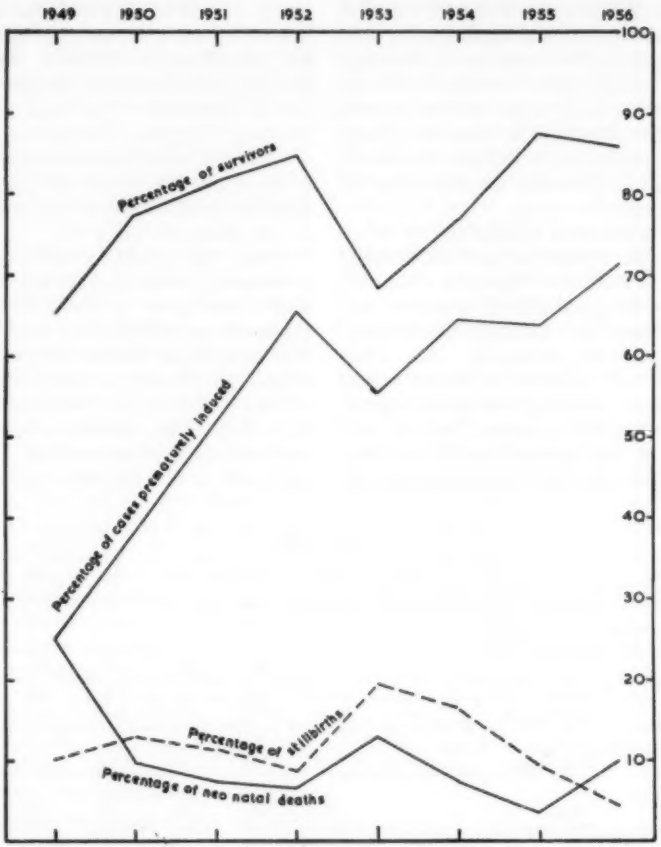

FIG. 2

Survival rates, all cases treated in Brisbane Women's Hospital during successive years, including those born before arrival.

Not only is this true for the total number of infants presenting for treatment at the Brisbane Women's Hospital (Fig. 2) but it also holds good for all cases born in the Brisbane Women's Hospital itself (Fig. 3).

The increase in total survivals, which parallels the increase in the percentage of prematurely induced infants, is due to a rise in the number of infants salvaged which would have been stillborn or severely affected at term, as can be seen from the graphs for neonatal deaths and stillbirths which run opposite to those for percentage survivors and percentage of prematurely induced infants.

It can be seen that the lines for percentage survival and percentage of infants induced lie closer together as the percentage of infants prematurely induced increases. This is what one would expect because there will always be some losses due either to stillbirth, prior to four weeks from the expected date of confinement, or to hydrops.

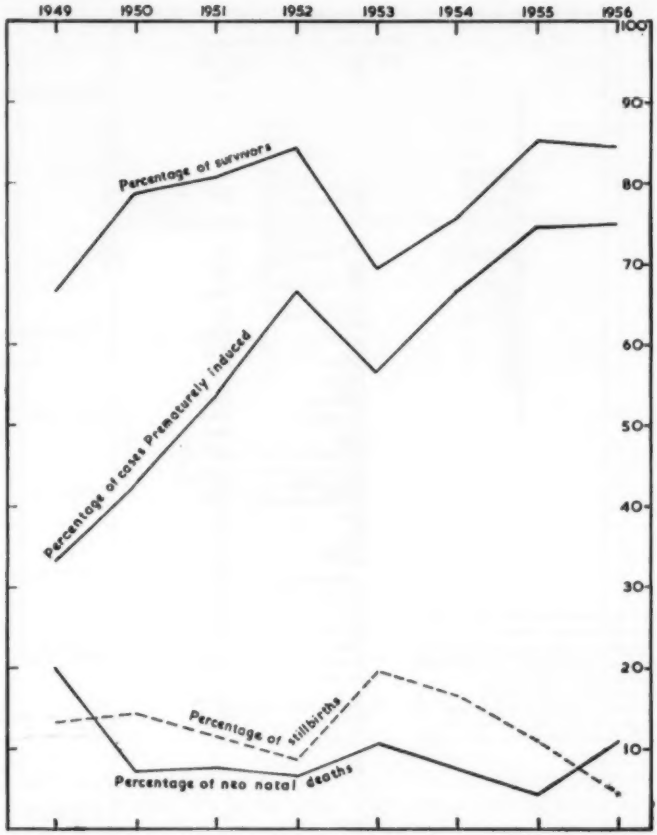

FIG. 3
Survival rates, all cases born in Brisbane Women's Hospital during successive years.

Mollison and Cutbush (1949) published a scattergraph constructed from normal and erythroblastotic cord haemoglobin values and showed how a high mortality is associated with low cord haemoglobin values.

Figure 4 is a similarly constructed scattergraph in which the cord haemoglobin value of 130 normal infants is compared with the cord haemoglobin or peripheral haemoglobin values (if the cord haemoglobin was unavailable) of all infants which were treated by exchange transfusion during the two periods under discussion.

This scattergraph gives a good comparison between the normal values and those for erythroblastotic infants. It can be seen that the normal values are similar to those published by Mollison and Cutbush. It can also be seen that, although a high mortality is associated with a low cord haemoglobin value, many infants with low initial haemoglobin values survived with early induction whereas only 2 of those which had been born at term with cord haemoglobin values below 7·5 g. survived. The higher survival rate among infants with low cord haemoglobin values

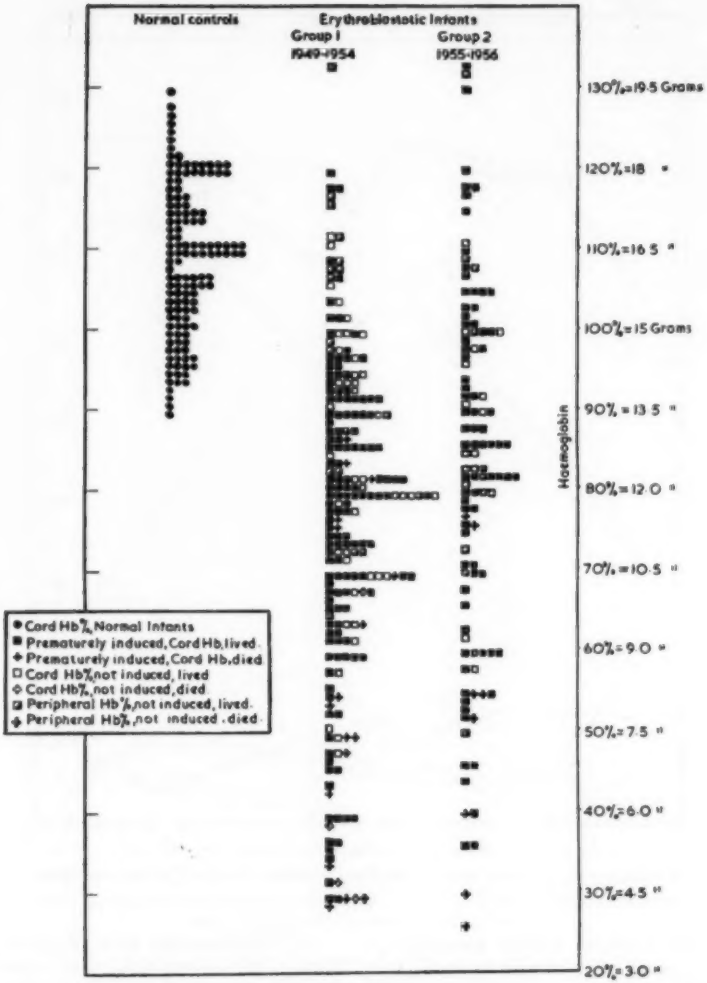

FIG. 4
Cord haemoglobin values.

(as compared with Mollison and Cutbush) is presumably due to (1) early induction, (2) large initial transfusion soon after birth.

In Figure 5 a scattergraph of 125 normal cord serum protein values (obtained by the copper sulphate method) is compared with the cord serum protein values of erythroblastotic infants taken during the years under review. In those cases where haemolysis had occurred in any of the specimens taken, the specimen was discarded. Enough material is available, however, to indicate that erythroblastotic infants have in

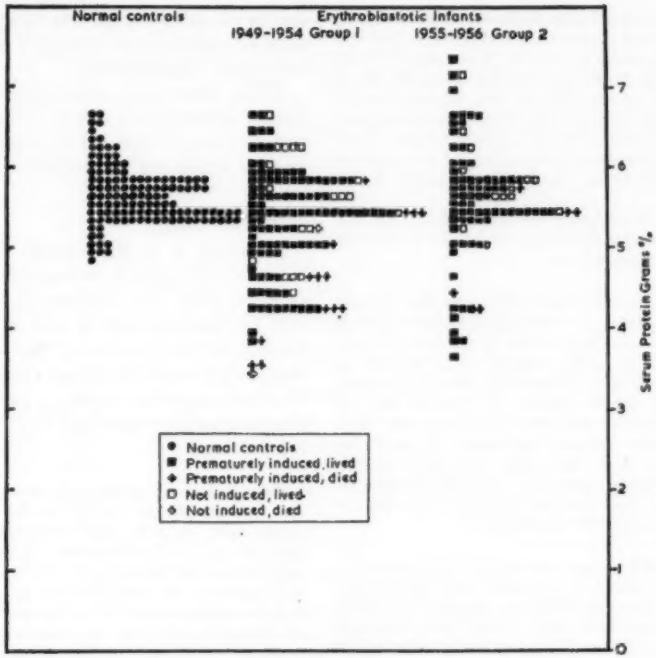

FIG. 5
Cord serum protein values.

general lower cord serum protein values than normal infants and that, among the group with the lowest values, there is a high mortality, possibly brought about by interference with liver function by direct action on the liver cells by maternal antibodies, by subsidiary sites of erythropoiesis, or by haemolysis and prematurity, and resulting in death on account of failure to excrete bilirubin or in some other way.

Cases Admitted to Brisbane Children's Hospital

Fifteen infants were admitted to the Brisbane Children's Hospital between 1st January, 1949 and 31st December, 1956 at varying times from two to fifty-two days from the date of birth. All these infants survived and although some of them might reasonably be admitted into the two groups already discussed they have been kept together because:

(1) The inclusion of a few of them among the other two groups would not make any significant difference to the findings already discussed.

(2) The maternal anti Rh antibody titres at or shortly after birth, and the haematological findings of the infants at or shortly after birth are lacking.

Inclusion in the various groups for purpose of analysis is therefore impossible.

In general this group of infants is one in which the likelihood of erythroblastosis had not been envisaged, and the infants were transferred to the Brisbane Children's Hospital for treatment from other hospitals when it became apparent that their post-natal condition was not normal.

As might be expected the clinical signs and symptoms varied immensely. A few examples will serve to indicate how confusing the signs may be when the condition is unsuspected.

Case 1. W.L.G., a full-term 6 pounds 2 ounces female infant was admitted fourteen days after birth. She was very white, with a haemoglobin of 17 per cent (2·55 g.) and dyspnoeic on admission. She was given 85 ml. of concentrated red blood cells (O Rh negative) into a scalp vein on admission and 76 ml. of concentrated red cells the next day and she made a good recovery. There was no history of neonatal jaundice in this case and she was subsequently found to be blood group A Rh positive.

The mother's blood group was Rh negative, she had albumin agglutinating antibodies to a titre of 1/8 and this was her first pregnancy.

Case 2. S.B., a full-term male infant weighing 7 pounds 4½ ounces was admitted thirteen days after birth, ghastly white and dyspnoeic. The Hb. was 16 per cent (2·4 g.). He was given 50 ml. O Rh negative blood through an intravenous cannula and subsequently 200 ml. of slightly shaken up blood during three hours. The next day the haemoglobin was 101 per cent (15·15 g.) and slight jaundice developed. He was discharged in good condition in fourteen days. The mother had had one other normal infant and one miscarriage. She was Rh negative and had albumin agglutinating antibodies to a titre of 1/256 two weeks after the infant's birth.

Case 3. Baby B.S.M. was received fifty-two days after birth severely jaundiced. The jaundice had been present since soon after birth and the infant who was a 5 pounds 1 ounce male when born had already been transfused four times. His spleen and liver were very large and he was thought to be a case of congenital obstruction of the bile ducts. His mother had two other children, she was Rh negative and had albumin agglutinating antibodies to a titre of 1/256 when admitted with the baby.

The infant's jaundice faded after three months from birth by which time he had been given two further transfusions of 65 ml. and 89 ml. of O Rh negative blood (he was O Rh positive) into a scalp vein. He was discharged in good condition.

It is easy to see therefore how erythroblastosis foetalis can mimic the appearance of haemorrhage, congenital absence of the bile duct or even a chest complication and how necessary it is that maternal blood grouping be done in all cases of pregnancy and a search made for Rh antibodies if the mother should be Rh negative.

It is worth mentioning here that the vast majority of cases of erythroblastosis foetalis occurring in the Brisbane Women's Hospital have been due to sensitization to the D antigen of the Rh blood group.

Occasionally the presence of Anti C, Anti E, or Anti c has complicated the picture; nevertheless in all cases except one (due to Anti E) the chief or sole cause of mortality or morbidity has been Anti D antibodies.

There were two mild cases of haemolytic disease of newborn, due to Anti A and Anti B and one due to Anti M during the years under review. These are not included in this series.

A Record Infant

Although it is the custom in the Brisbane Women's Hospital to induce labour prematurely as soon (after the 36th week) as the maternal anti Rh antibody titre is 1/32 or above, it is not possible to say how many days earlier than the thirty-sixth week this might reasonably be done. The following case history in which a small baby was successfully transfused by one of us (D.L.W.) is of interest:

Baby J., was a 3 pounds 2½ ounces male infant who was induced 30 days prior to the expected date of confinement because the maternal anti Rh saline agglutinating antibodies were 1/64 and the albumin agglutinating antibodies 1/512. The mother had toxaemia of pregnancy. The cord Hb was 110 per cent (16·5 g.) and the serum protein 4·3 g. He was O Rh positive and the direct Coombs test was positive. He was given an exchange transfusion via the umbilical vein while lying in a humidicrib; 200 ml. of blood were withdrawn and 200 ml. of blood injected. He subsequently had to be transfused four times by scalp vein (40 ml., 40 ml., 55 ml. and 70 ml. being injected) because of a fall of haemoglobin, but apart from this his progress was uneventful.

Twins. In this series there were 4 twin pregnancies and in each case both babies were affected. Their progress did not differ from that of single pregnancies.

Caesarean section. Caesarean section has been performed 7 times but *only* for obstetrical reasons (toxaemia and placenta praevia). The clinical course of the infants treated was not affected.

Comparison with Other Workers' Published Series

The series shown in Table XIV may be used for purposes of comparison. The percentages are those worked out from the total number of presenting pregnancies whether stillbirths or live births reported by the authors concerned.

TABLE XIV

Author	Period	Total Number of Cases	Stillbirths		Neonatal Deaths		Survivors		Whether Early Induction was Practised
			Total Number	Per-centage	Total Number	Per-centage	Total Number	Per-centage	
Allen and Diamond (1954)	1.1.45 to 10.1.46	24	4	16·67	10	41·67	10	41·67	—
	11.1.46 to 3.1.49	68	11	16·18	16	23·53	41	60·29	—
	4.1.49 to 30.6.51	85	17	20·0	4	4·7	64	75·29	No
	1.7.51 to 30.6.53	64	16	25·0	2	3·12	46	71·87	No
Shelton (1955)		117	31	26·49	7	5·98	79	67·52	No
Kelsall and Vos (1955) ..		918	113	12·3	77	8·38	728	79·41	Yes
Group 1 this series (cases born in Brisbane Women's Hospital only)	1.1.49 to 31.12.54	214	31	14·48	19	8·87	164	76·63	Yes
All cases treated in Brisbane Women's Hospital (Brisbane Children's Hospital cases excluded)	1.1.49 to 31.12.54	227	31	13·65	23	10·13	173	76·21	Yes
Group 2 this series (cases born in Brisbane Women's Hospital only)	1.1.55 to 31.12.56	111	8	7·2	9	8·1	94	84·68	Yes
All cases treated in Brisbane Women's Hospital (Brisbane Children's Hospital cases excluded)	1.1.55 to 31.12.56	125	8	6·4	9	7·2	108	86·4	Yes

In the series of cases discussed here, all deaths have been regarded as due to, or chiefly due to, Rh incompatibility. No case has been excluded even in the presence of other abnormality.

It has not been possible to include the findings of Walker and Neligan (1955) in the tabulated cases above because stillbirths were not reported.

The findings of Mollison and Walker (1952) could not be fitted into the scheme because of the manner in which the controlled trials of various forms of treatment were carried out.

SEQUELAE

Evidence now available suggests that a high level of serum bilirubin is itself responsible for the destruction of nerve tissue. In a follow-up of all cases which had survived it was found that one infant who was admitted icteric and who was not treated by exchange transfusion developed spasticity of the lower extremities. One infant who was treated by exchange transfusion and later became jaundiced also showed spasticity. One infant (referred on the third day) became mentally retarded and another also referred on the third day became spastic. A fifth infant who was deeply jaundiced after exchange transfusion is now deaf. All these cases except one, and all cases of kernicterus, occurred between 1949 and 1954. It is to be hoped that with more frequent use of multiple exchange transfusions these distressing complications will cease to occur.

Consideration of the foregoing suggests that the treatment of erythroblastosis foetalis should be conducted along the following lines:

(1) The blood group and the type of each expectant mother should be determined.

(2) If found to be Rh negative, serial antibody tests should be carried out, e.g., at 12, 28, 32, 36, 38 weeks of pregnancy.

(3) Those found to have an antibody titre which is well below the dangerous level as

determined in each laboratory should be allowed to go to term.

(4) In those cases where a high (dangerous) maternal antibody titre is found, early induction should be carried out. An antibody titre of 1/32 is an indication for induction, provided the infant is viable.

(5) When the infant is born, it should be examined and its blood group, cord haemoglobin, cord serum protein (and, if possible, cord serum bilirubin as well) should be ascertained and finally the direct Coombs reaction should be determined. An erythroblast count is of interest, but it is of little prognostic significance.

(6) If the maternal antibodies are known to have been at a low titre prior to delivery (0–1/4) the infant may be left alone, even if found to be Rh positive with a positive direct Coombs reaction. Such infants would, in all probability, have a high cord haemoglobin value. These infants should be examined at two- to three-weekly intervals and treated by simple transfusion if they become anaemic and do not respond to iron tonic.

(7) If the infant is Rh positive Coombs positive and maternal anti Rh antibody titre is known to have been 1/8–1/16, the infant should be given an exchange transfusion at birth, preferably by the umbilical cord route, using one bottle of blood even if the cord haemoglobin is above 15 g.

(8) If the maternal antibodies are known to have been at a dangerously high titre prior to the birth of an erythroblastotic infant, a complete 90 per cent exchange transfusion must be done.

(9) If, following exchange transfusion, the infant manifests signs of kernicterus, such as severe jaundice, head retraction, irritability or convulsions, vomiting, hyperpyrexia, or if the serum bilirubin level is found to be above 15 mg. per cent a second exchange transfusion should be done and if the symptoms do not abate it may be necessary to do a third exchange transfusion.

(10) If a jaundiced Rh positive infant should be admitted to hospital within 5 days after birth with a haemoglobin of above 15 g. and a positive direct Coombs test, it is preferable to do an exchange transfusion rather than wait for the maternal antibody titre to be determined as this will cause unnecessary and dangerous delay.

(11) Erythroblastotic infants admitted to hospital after 5 days from birth may be considered to have had a test period during which kernicterus did not develop and may be treated by repeated small injections of blood (10–12 ml./pound of body weight) for the treatment of anaemia.

(12) Grossly anaemic infants would be best treated with a massive initial transfusion of concentrated red cell suspension, preferably administered by a cannula inserted into a saphenous vein.

All infants treated should be under a 3-month period of surveillance and should be transfused if the haemoglobin level cannot be maintained by haematinics.

(13) For those infants destined to die *in utero* before the 36th week of pregnancy, there is at present no satisfactory form of treatment.

(14) Erythroblastotic infants, in whom a blood factor other than the Rh (particularly the D antigen of the Rh group) is involved, may be treated along similar lines.

It should be possible in a large hospital to estimate foetal size and weight with the assistance of X-rays and obstetrical experience.

It is worth recording at this stage that no maternal mortality or morbidity has resulted which can be attributed to the manipulations necessary for early induction in the Brisbane Women's Hospital during the years under review.

Summary

An analysis of all cases of erythroblastosis foetalis treated between 1949 and 1956 in the Brisbane Women's Hospital and Brisbane Children's Hospital is presented.

It is shown that there is a sudden rise in infant mortality when the maternal anti Rh antibody titre reaches a critical level. The use of this level as a criterion for early induction of labour has resulted in a substantial reduction in both the stillbirth and neonatal death rates.

Acknowledgments

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A PRELIMINARY INVESTIGATION OF THE CHANGES IN STEROL DISTRIBUTION IN RELATION TO LIPOPROTEINS IN PRE-ECLAMPSIA

BY

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THE significance of changes in the blood lipids and their possible effects on the normal physiology of pregnancy are not yet known, but it is believed that a consideration of such changes may lead to a better understanding of some of the pathological states associated with pregnancy. The blood lipids may be defined as substances which are totally soluble in ether-alcohol, i.e., "neutral fats" (glyceryl esters of higher fatty acids), fatty acids, steroids, phospholipids and cerebrosides.

In view of the unusual distribution of the lipoproteins now known to exist in normal pregnancy it was thought expedient to determine their distribution in patients suffering from toxaemia of pregnancy, both pre-eclampsia and essential hypertension. It was also thought expedient to study a control group of normal patients concurrently with the cases of pre-eclampsia.

The balance of the serum proteins in normal blood ensures a relatively stable colloidal solution. However, since the circulating lipids depend on the serum proteins for their dispersion, alteration of the albumin/globulin ratio will be reflected in reduced stability of the lipids, with a tendency to deposition in unusual sites and amounts (atherosclerosis, fatty liver). Furthermore, these changes in the displacement of the serum proteins and lipids are known to cause increases in the erythrocyte sedimentation rate, increases in blood viscosity, abnormalities in blood clotting, and also alterations in the permeability of cells and cell membranes.

Normal pregnancy is associated with a fall in the serum albumins, a compensatory rise in the serum globulins and a rise in all the lipids. Thus, any contributory factor (for example, diet) which may cause a further shift in the albumin/globulin ratio below the normal physiological mean for pregnancy may result in a diminished stability of the colloids and hence an increased tendency to thrombus formation, particularly if the high-molecular-weight beta globulins are excessively loaded with fat (beta-lipoproteins).

METHODS

0·1 ml. serum approximately three to six hours old was applied evenly over a distance of 3·0 cm. to Whatman No. 3 MM filter paper, width 4 inches. The serum proteins were then separated by electrophoresis, using diethyl-barbiturate buffer, pH 8·6, ionic strength 0·075. Through each paper strip a current of 0·3 mA per cm. width of paper was run for approximately 17 hours. Fresh buffer was used for each separation. A marker, 3 cm. wide, was also run on the same paper for subsequent detection and correlation of the protein and lipid bands.

The paper was subsequently dried for 30 minutes at 110° C. and then cut up into strips, 1 cm. wide, and the amount of cholesterol on each strip was extracted and estimated by a modification of the method used by Boyd (1954). All the cholesterol determinations were read against a reagent blank. A strip of the filter paper, 1 cm. wide, and taken from either end

of the paper, was used as a paper blank. A recovery of 85–110 per cent cholesterol was usually obtained. The concentrations of the alpha and beta-lipoproteins (μg. cholesterol per 0·1 ml. serum) were then determined and the beta:alpha-lipoprotein ratio ascertained. The inner 1 cm. strip showing the lowest amount of cholesterol was taken as the point of separation of the alpha and beta-lipoproteins.

The cholesterol was estimated on a Unicam SP. 600 spectrophotometer using 10 mm. cuvettes at 635 mμ. The total serum cholesterol was estimated by the method of Sackett (1925) using 10 mm. cuvettes at 635 mμ. The lipids were detected by the method of Rosenberg (1952) and the protein staining and quantitative evaluation by the method of Jencks (1955), using an "EEL" scanner.

Material

In all, 122 patients were studied. Of the 110 patients investigated later in pregnancy, between the 29th and 42nd weeks, 64 were deemed to be cases of normal pregnancy and all of these patients were primigravidae between the ages of 18 and 35 years. There were 32 patients who developed the clinical features of pre-eclampsia. Most of these patients were primigravidae whose ages varied from 18 to 38 years. There were 9 patients with essential hypertension complicating pregnancy and 5 cases of essential hypertension with superimposed pre-eclampsia. The remaining 12 patients were normal primigravidae, between the ages of 20 and 30 years, who were studied between the 10th and 15th weeks of pregnancy.

The duration of pregnancy was calculated to the nearest week from the first day of the last menstrual period and the estimation was confirmed by clinical examination.

Results

Group I. Normal Pregnancy

All the 64 normal patients had an entirely uncomplicated pregnancy. The blood pressure remained at less than 140/90 mm./Hg, there was no albuminuria and no more than a trace of ankle oedema.

These patients were investigated between the 31st and 42nd week of pregnancy. Fifty of the patients were studied between the 34th and 38th weeks. In view of the possible implications of variations in weight gain during pregnancy, the results are shown in Table I, in relation to the total weight gain for the pregnancy. The results of the group of 12 cases investigated between the 10th and 15th week are also recorded in Table I. The distribution of the cholesterol between the beta and alpha-lipoproteins rose

TABLE I

Mean Values and Standard Deviations of β:α Lipoprotein Ratio and Total Serum Cholesterol in 64 Normal Pregnant Women with Widely Varying Total Weight Gains

Total Weight Gain (Pounds)	Duration of Pregnancy (Weeks)	No. of Cases	β:α Lipoprotein Ratio		Total Cholesterol mg./100 ml. Serum	
			Mean	Standard Deviation	Mean	Standard Deviation
	10–15	12	1·9	±0·15	222	±38·8
10–14		2	2·7		266	
15–19		9	3·1		276	
20–24		14	3·7		265	
25–29	31–42	20	3·6		288	
30–34		10	3·9		266	
35–39		7	3·7		290	
40–44		2	2·3		267	
		64	3·5	±1·32	277	±50·1

from a mean of 1·9:1±0·15 between the 10th and 15th weeks to a mean of 3·5:1±1·32 between the 31st and 42nd weeks of pregnancy. This difference is significant ($P<0·01$). The mean total cholesterol for the whole group was 277 mg./100 ml.±50·1, in the last trimester, as compared with 222 mg./100 ml.±38·8 between the 10th and 15th week, a rise of 25 per cent. The mean difference of 55 mg./100 ml. is statistically significant ($P<0·01$).

From a study of the results of these normal patients in relation to total weight gain for pregnancy there would appear to be a trend to higher lipoprotein ratios in women with an increasing and excessive weight gain. However, in the number of patients so far investigated no statistical difference can be shown. It is felt, however, that the results would justify further investigation of the possible relationship between weight gain and the distribution of the serum lipids between the alpha and beta-lipoproteins.

Group II. Pre-eclampsia

This group of 32 patients includes moderate and severe cases of pre-eclampsia. All showed the usual clinical features of the disease, i.e., sustained elevation of blood pressure over 140/90 mm. Hg, oedema and albuminuria (absent in two cases). In 14 out of 19 (approximately 74 per cent) of the patients in whom a detailed antenatal record was available there was also evidence of short-term excessive weight gain preceding the onset of the classical clinical features of pre-eclampsia. The significance of this observation is dependent upon the possibility that rapid changes in the state of hydration of the body may be related to the binding of water on protein that previously bound lipid. When investigated all the patients were "in-patients" who had been confined to bed for periods varying from 24 hours to 1 week. None of the patients had been given any specific treatment with, for example, hypotensive drugs or modified diet.

The estimations were performed between the 29th and 40th weeks of gestation. Twenty-two patients were between 34- and 38-weeks gestation. The mean total cholesterol was 282 mg./100 ml.±56·6 and the mean beta/alpha lipoprotein ratio was 4·6:1±2·15 (Table II). This rise in the beta/alpha lipoprotein ratio as compared with the normal group is statistically significant ($P \simeq 0·01$).

The concentration of the cholesterol in the alpha-lipoproteins was usually decreased. The decrease was observed in most of the patients with pre-eclampsia, and would appear to be related to the amount of protein lost in the urine, i.e., hypoalbuminaemia. Moreover, there was often a sharp increase in the concentration of the cholesterol migrating with and in front of the beta-globulins. The increase was present largely in the pre-beta-lipoprotein band (Smith, 1957) and the beta-lipoprotein band.

TABLE II

Mean Values and Standard Deviations of β:α Lipoprotein Ratio and Total Serum Cholesterol in Women with Pre-eclampsia and/or Essential Hypertension

Pregnancy	Duration of Pregnancy (Weeks)	No. of Cases	β:α Lipoprotein Ratio		Total Cholesterol mg./100 ml. Serum	
			Mean	Standard Deviation	Mean	Standard Deviation
Pre-eclampsia:						
Moderate	29–40	19	4·4		267	
Severe		13	4·9		297	
		32	4·6	±2·15	282	±56·6
Essential hypertension ..	36–39	9	4·5	±1·01	295	±63·4
Essential hypertension with superimposed pre-eclampsia	32–36	5	4·5		251	

Group III. Essential Hypertension

All 9 patients had a sustained blood pressure of over 140/90 mm. Hg before the 20th week of pregnancy. The 9 patients were investigated between the 36th and 39th week of pregnancy. The mean cholesterol was 295 mg./100 ml. $\pm$63·4 and the mean beta/alpha lipoprotein ratio 4·5:1 $\pm$1·01 (Table II). This ratio is very similar to that found in pre-eclampsia and the rise in ratio as compared with the normal series is statistically significant, $P \simeq 0{\cdot}01$.

Group IV. Essential Hypertension with Superimposed Pre-eclampsia

These 5 patients with superimposed pre-eclampsia, between 32- and 36-weeks gestation, had a mean total cholesterol of 251 mg./100 ml. and a mean beta/alpha lipoprotein of 4·5:1 (Table II). This rise in the lipoprotein ratio is statistically significant, $P \simeq 0{\cdot}01$, as compared with the normal control series.

Consideration of Results

(a) *Beta/Alpha Lipoprotein Ratio*

The results obtained in this and other studies (Oliver and Boyd, 1955; Watson, 1957) would appear to show that in pregnancy a much greater proportion of the serum lipids is carried on the beta fraction of the globulins than on the alpha globulins. Oliver and Boyd found that the beta/alpha lipoprotein ratio rose from 2·0:1 in non-pregnant women to 5·0:1 in pregnant women at the 32nd week and thereafter fell gradually to a figure of 4·0:1 at the 20th post-partum week. Our results, in the main, confirm this finding although the ratio did not exceed 3·5:1 in the normal group. This discrepancy in results may be due to the fact that there appears to be a trend to higher beta/alpha ratios in women who gain weight excessively during pregnancy and the 12 normal primigravidae studied by Oliver and Boyd had a mean weight increase of 36$\pm$8 pounds. Watson noted a 31 per cent increase in the mean beta/alpha lipoprotein ratio in 5 women at the 33rd week of pregnancy who gained weight in excess of his normal group. In our study it was noted that the beta/alpha lipoprotein ratio tended to be slightly higher in many of the women who gained weight excessively during pregnancy, but who were otherwise normal (Table I). Watson found also that there was a significant rise in the lipoprotein ratio from a mean level of 1·14:1 at the 13th week to 1·85:1 at the 37th week. It should be noted that these ratios were calculated as lipoprotein and not in terms of cholesterol alone. Watson thought that there might be a significant fall in the beta/alpha ratio during the week preceding delivery.

(b) *Total Serum Cholesterol*

In our study, the total serum cholesterol in normal and pre-eclamptic women showed no significant difference. However, in 6 out of the total of 32 patients with pre-eclampsia the total cholesterol was significantly lower than the mean for the group. In these 6 cases the mean total cholesterol was 239 mg./100 ml. $\pm$40·1. This low cholesterol was also associated with a low lipoprotein ratio (mean 2·3:1) which was significantly lower than the ratio found in the normals and in the total group of pre-eclamptics. Among the cases of pre-eclampsia this sub-group of 6 patients who had atypical cholesterol distribution showed no clinical features which distinguished them from the other cases of pre-eclampsia. The laboratory findings are, therefore, not readily explained.

Discussion

Although the possible causes of the changes observed in the circulating lipids of pregnancy have been fully reviewed by Oliver and Boyd (1955) and Watson (1957) it might prove useful to discuss one or two points in the light of newer knowledge.

Oestrogens and the Circulating Lipids

The well-known fact that women during menstrual life are relatively immune from coronary atheroma led to the observation that the administration of oestrogens to hypercholesterolaemic men could depress the blood cholesterol to near-normal limits. Following the menopause the incidence of coronary thrombosis in women rises *pari passu* with a

rising blood cholesterol. Much is now known of the excretion of oestrogens during pregnancy. Brown (1957) has shown that the total urinary oestrogen excreted (in terms of oestradiol, oestrone and oestriol) at the ovulatory peak of the normal menstrual cycle, at which time conception occurs, is of the order of 80 μg. per day. By term this has risen to 40 mg. per day. There is no terminal fall in oestrogen excretion which, in fact, continues to rise until delivery. Brown has computed that the placenta secretes as much as 30 mg. of these oestrogens a day by the 28th week, and this rises to about 50 mg. at term. The maximum levels of serum cholesterol and the increase of beta lipoproteins are reached by about the 30th week, yet at this time relatively enormous quantities of oestrogens are being excreted. There is no obvious explanation of this apparent discrepancy. Watson (1957) has suggested that the answer may be simply one of transport. It is known that about two-thirds of the blood oestrogen is transported as an oestrogen/lipoprotein complex. If, as appears likely, most of this is carried on the beta globulins, then an increased beta/alpha ratio might be expected in pregnancy. Two facts would appear to make this hypothesis untenable. Firstly, the increased beta/alpha ratio persists for some weeks into the puerperium when it is known that oestrogen excretion is as low as that of a post-menopausal woman. Secondly, if there is a fall in the beta/alpha ratio in the last weeks of pregnancy, then this is associated with a rising and not a falling oestrogen secretion. The significantly higher beta/alpha ratio found in pre-eclampsia as compared with normal pregnancy cannot be explained readily. It is probable that in cases of pre-eclampsia there is decreased placental secretion and, therefore, decreased excretion of oestrogens. There is no evidence that the kidney is failing to excrete oestrogens in these patients.

Progesterone and Pregnanediol

Progesterone when given to men does not apparently affect the blood lipids (Oliver and Boyd, 1956). During pregnancy the amount of progesterone excreted as sodium pregnanediol glucuronide increases from about 2 mg. per day at the time of conception to about 40 mg. at the 38th week when there is usually a fall in excretion (Klopper, Michie and Brown, 1955). Little is known of the blood progesterone levels during normal pregnancy but they are said to be low (Zander, 1954). Teleologically one might explain the hypercholesterolaemia of pregnancy by the need of many organs for an ample supply of cholesterol. In pre-eclampsia there is in many patients a fall in pregnanediol excretion well before term and at a time when the beta/alpha lipoprotein ratio remains high.

Plasma Proteins and the Blood Lipids

Although there is an increase in the total circulating protein in normal pregnancy due to an expansion of the blood volume, yet there is a relative fall in the plasma protein concentration by about 1 g. per 100 ml. of plasma. This fall is mainly due to the fall in the albumin fraction (water-soluble), for all the globulins (water-insoluble) show an increased value in pregnancy. According to Mack (1955) the increase in the globulins in normal and pre-eclamptic pregnancy is largely of the alpha type, with no significant change in the beta-globulin concentration. However, this does not give an accurate evaluation of the beta-lipoprotein concentrations, since small changes in the protein distribution may be associated with considerable variation in the lipid levels carried by all the protein fractions, particularly alpha and beta-globulins. Thus, the increased lipoprotein ratios found in pre-eclampsia may not necessarily be associated with a significant increase in the beta-globulin concentration, but rather with a fall in concentration of the albumin.

Dietary Features

Studies on the blood lipids in pregnancy have so far largely been confined to women taking an ordinary American or European type of diet. There is apparently a trend towards higher ratios in women who gain weight excessively and, of course, the majority of pre-eclamptic patients have greatly increased weight gains. There is some evidence that severe accidental haemorrhage is found more frequently in women on a poor diet. Whether or not there is any relationship between a dietary deficiency of essen-

tial fatty acids due to the demands of the growing foetus and the blood lipids during pregnancy is as yet unknown, but well worthy of study.

Elevation of the blood cholesterol and a raised beta/alpha lipoprotein ratio are characteristic changes in conditions associated with atheroma of the larger vessels. Thus, in coronary disease, long-standing diabetes and myxoedema, atheroma is not uncommon. Obstetricians have long been baffled by the possible aetiological factors which determine an accidental haemorrhage or which lead to placental degeneration. There is little doubt, however, that the latter condition is due to a reduction in the blood supply to the choriodecidual space and in established pre-eclampsia this may be reduced by a half to two-thirds. This fall in blood supply is presumably determined by a reduction in the number or the calibre of the spiral arterioles. Thanks to the work of Boyd (1957) a great deal is now known about the histology of these vessels in normal pregnancy, at least in the earlier months. Little is known, however, of their exact anatomy in pre-eclampsia. Data produced by Zeek, Assali and Hertig (1955) has suggested that the lesion in the spiral arterioles in pre-eclampsia (or in accidental haemorrhage) may be in the nature of an "atherosis"—that is, there is considerable thickening of the intima with the deposition of cholesterol and other fatty substances in the subintimal layers and around the vessel. The spiral arteriole occupies a peculiarly vulnerable position in the decidua basalis and is ill-supported by this layer. That degeneration and rupture occur in what has hitherto been a perfectly normal pregnancy is not at all surprising. Whether the distribution of the lipids in the blood in pregnancy and pre-eclampsia could determine or even accelerate this degeneration is a moot point. Atheroma of the classical variety affects the larger vessels and the condition referred to by these authors as "atherosis" would not necessarily be accepted by all pathologists. In some specimens, available in the Department of Obstetrics in Edinburgh, a process of simple thrombosis has clearly determined the occlusion of a spiral arteriole.

That the hypercholesterolaemia of pregnancy could accelerate placental degeneration in the layers of the chorionic epithelium is another possibility. Cholesterol does not pass readily across the chorionic membrane and the total serum cholesterol in the umbilical vein is only about one quarter of that found in the maternal blood. Histochemical methods have demonstrated the presence of cholesterol and fatty substances in the human decidua basalis and the chorionic epithelium, and this is apparently increased in postmature and pre-eclamptic placentae. Evidence that there is an increase in histologically demonstrable fat in the villi and decidua of the pre-eclamptic placenta is as yet not very convincing. This is not surprising, since the fat is bound to protein.

In this preliminary communication it is not possible to draw any definite conclusions regarding the full significance of the hypercholesterolaemia and of the increased concentration of beta-lipoprotein found in normal and pre-eclamptic patients. However, Rutstein, Ingenito, Craig and Martinelli (1958) found in tissue-culture studies of human aortic cells in a medium containing human blood-serum, that when cholesterol bound to beta-lipoprotein was added to the culture medium, the amount of lipid deposited in the cells was proportional to the amount of cholesterol added. This may be a factor in cases of pre-eclampsia and accidental haemorrhage. Moreover, it is possible that some of the lipid changes found in patients with pre-eclampsia are due to a deficiency in circulating albumin.

Summary

(1) The total serum cholesterol in pregnancy rises from the early weeks and reaches a maximum level at about the beginning of the third trimester (222 mg./100 ml. to 277 mg./100 ml.).

(2) There is no evidence of any significant difference in the total cholesterol in normal (277 mg./100 ml.) and pre-eclamptic pregnancies (282 mg./100 ml.).

(3) A significant increase in the beta/alpha lipoprotein ratio occurs during normal pregnancy (1·9:1 to 3·5:1). An additional significant increase occurs in patients with pre-eclampsia (4·6:1).

(4) A significant increase in the beta/alpha lipoprotein ratio occurs in patients with essential hypertension (4·5:1).

(5) A significant increase in the beta/alpha lipoprotein ratio also occurs in patients with essential hypertension with superimposed pre-eclampsia (4·5:1).

(6) The implications of this change in the serum lipids in relation to pre-eclampsia and accidental haemorrhage are discussed.

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THE USE OF HIGH CONCENTRATION OXYTOCIN INTRAVENOUS DRIPS IN THE MANAGEMENT OF MISSED ABORTION

BY

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FOR many years the search for a substance whereby the uterine muscle could be stimulated and labour induced, or contractions strengthened, taxed the minds of obstetricians and physiologists alike. With the discovery of the oxytocic activity of an extract from the posterior pituitary gland by Dale in 1906 it was thought by many that the search had ended. In 1909 Blair Bell used this extract in a human patient in the management of labour complicated by an atonic uterus.

For a long time thereafter the whole extract ("Pituitrin") or its oxytocic component ("Pitocin") were used either by subcutaneous or by intramuscular injection, but, given by these routes, there was no effective control of the amount of extract circulating in the blood stream and acting on the uterine muscle. However, in 1943 Page reported the use of pitocin by means of an intravenous infusion in uterine inertia; and in 1948 Theobald *et al.* published the results of a large series of cases in which intravenous pituitrin drip was used in the induction of labour and in the treatment of uterine inertia. Since then there has been a very large number of papers describing the use of intravenous oxytocin drips in these circumstances, but little mention has been made of the technique in the treatment of missed abortion.

Hitherto various methods of managing missed abortion have been employed:

(*a*) A policy of awaiting the natural expulsion of the dead foetus and placenta.

(*b*) "Medical induction", such as a course of oestrogen used either alone or as a sensitizing agent prior to the use of quinine and intramuscular pituitrin.

(*c*) Surgical evacuation of the uterus either by curettage (with or without initial dilatation of the cervix by laminaria tents) or by hysterotomy.

The first method may well be indicated in certain cases where the diagnosis remains in doubt. Every obstetrician can remember cases in which an early provisional diagnosis of missed abortion has been followed by the delivery of a healthy child some 5 or 6 months later and in many cases there is no doubt that a further period of observation is advisable before accepting the diagnosis. In such cases the uterus may empty itself during the period of observation, thus solving the problem.

Once the diagnosis is confirmed the majority of obstetricians favour some form of active treatment, there being disadvantages to the alternative policy of watchful expectancy. These disadvantages have been concisely stated by Corbett (1958) as "inconvenience, varying degrees of mental distress, continued abeyance of reproductive function, restriction of full activity and finally the constant dread of the abortion completing itself awkwardly in time or place".

Moreover, reports have been appearing in the literature showing that some cases of missed abortion are associated with severe haemorrhage and hypofibrinogenaemia (Barry, Geoghegan and Shea, 1955; Quinn and Harper, 1955). This finding alone would appear to be a strong argument in favour of active treatment.

It is generally desirable to effect delivery as soon as possible after the diagnosis is confirmed, thus alleviating the mental distress associated with the patient's knowledge that her baby is dead. Methods of "medical induction" are unreliable and tend to lead to rather protracted treatment. Martin and Menzies (1955) in a critical re-evaluation of the role of oestrogen therapy have shown that in those cases where such therapy is successful the induction-delivery interval was on average 7·7 days and that the success rate was only 73 per cent.

Quinine and intramuscular pituitrin, either separately or in combination, seem to be no more successful.

Evacuation of the uterus vaginally with or without the prior use of laminaria tents is a satisfactory method of treatment, but in cases where the uterus is larger than a three-months gestation there is always the danger of excessive haemorrhage. Furthermore, the introduction into the uterus of foreign material in the form of laminaria tents carries with it a greater risk of infection.

Finally, in some cases it has been found necessary to carry out abdominal hysterotomy. Bivens (1957) describes 23 cases of missed abortion and in 3 has employed abdominal hysterotomy, and one of the 30 cases described by Fisher (1953) was also treated in this way.

Intravenous pitocin drip has been suggested as a method of terminating pregnancy in cases of missed abortion. Bivens (1957) advises this form of treatment, but does not describe the dose used and is not impressed by its reliability. O'Driscoll and Lavelle (1955) mention its use in one case. They used 5 units of pitocin per pint (540 ml.) of glucose solution at a rate of 120 drops per minute. After 3 days of this treatment no change in the state of the cervix had been achieved and one month later they felt it advisable to carry out hysterectomy. Ryan (1958) employed the method in 3 cases. Pitocin was given in a concentration of 2·5 units per pint (540 ml.) at a rate between 40 and 80 drops per minute. The technique he employed "proved of no value".

During our investigation of pitocin drip for the induction of labour we found that in the less advanced pregnancies a higher concentration of oxytocin than usual was generally required to ensure success. It was considered therefore that pitocin drip in a relatively high concentration might prove an effective method of terminating pregnancy in missed abortion.

Method

Early on the day selected an intravenous drip of 6 per cent dextrose solution is set up with the needle in a forearm vein situated in such a way as to allow the patient maximum freedom of movement. As soon as the drip is running satisfactorily 10 units of pitocin are injected into the dextrose solution, which is thoroughly mixed by shaking. The pitocin solution is allowed to run in at the rate of 25 drops per minute. Thereafter the strength of the solution is gradually increased from 10 units per pint (540 ml.) to 100 units per pint (540 ml.), the rate of flow being frequently adjusted to give a constantly increasing dosage of pitocin. Should the patient experience regular painful contractions the concentration and rate are no longer increased and sedation with pethidine or morphine may be given as required. In some cases no "pains" will be felt by the patient and no contractions will be detected by the examining hand. Under these circumstances the dosage is gradually increased throughout the day. The drip is discontinued in the late evening if abortion has not already occurred. If the patient does not abort during the first day she may do so during the ensuing night, but if nothing has happened by the following morning the drip is resumed with a rather lower concentration of pitocin than was in the last bottle the previous evening. In some of the earlier cases, as will be seen, the drip was not continued on the following morning and further drips were required 3 to 7 days later.

Results

This method of treatment has been employed so far in 18 cases which represent the total number of missed abortions occurring during or after the twelfth week of gestation in Professor Kellar's Unit of the Simpson Memorial Maternity Pavilion during the past 3 years. The estimated duration of foetal death varied between 3 and 14 weeks.

TABLE I

Case No.	Age	Parity	Estimated Maturity at Foetal Death in Weeks	Maturity at Delivery in Weeks	Duration of Intra-uterine Death in Weeks	Induction Delivery Interval (hrs. min.)	Highest Concentration (units/pt)	Estimated Total Dose (units)	Evacuation Required	Remarks
1	28	3+1	16	26	10	48.00	5	10	Yes	—
2	32	4+0	20	25	5	7.00	20	20	Yes	Previous drip described in text.
3	24	3+0	26	29	3	15.00	35	90	Yes	Previous drips described in text.
4	32	6+0	18	25	7	20.00	60	80	Yes	—
5	33	2+1	16	26	10	0.45	40	10	No	Previous drip described in text.
6	36	3+0	18	24	6	10.00	40	40	No	—
7	23	1+0	?	16	?	24.00	80	100	Yes	Admitted as threatened abortion.
8	25	3+0	22	26	4	8.45	20	20	No	—
9	30	3+2	12	21	9	11.35	10	20	Yes	This patient had a 20 ounce fluid blood loss during evacuation of the uterus.
10	23	0+0	22	28	6	23.15	80	120	Yes	Anencephalic foetus.
11	25	0+0	18	24	6	10.15	80	60	No	—
12	27	2+0	16	30	14	31.15	100	350	No	Foetal suicide—cord tight round leg.
13	25	0+0	26	29	3	24.00	60	60	No	—
14	43	5+2	16	19	3	9.35	40	100	No	—
15	32	2+0	24	28	4	12.00	10	30	No	Iso-immunization.
16	26	1+0	12	21	9	33.05	100	150	No	—
17	34	2+1	24	27	3	10.30	40	60	No	Iso-immunization. The same patient as No. 15.
18	29	2+0	?	?	?	9.30	80	140	Yes	Hydatidiform mole.

The results are summarized in Table I. In the last 13 cases delivery was achieved in all but 2 patients within 24 hours of commencing the drip. Of the exceptions one took 31¼ hours and was in fact the patient in whom the foetus had been dead for the longest time, namely 14 weeks. In the other the foetus was passed 21¼ hours after commencement of the drip, but as the placenta failed to follow another drip was employed 11 hours later. The placenta was passed 50 minutes after commencement of the second drip. There was no bleeding.

Three of the earlier cases, Nos. 2, 3 and 5 required further drips 3 to 7 days after the initial attempt, but as already stated that was before it was realized that it was advisable to resume the drip the following day in the event of failure. Case 2 was given an intravenous drip of an experimental oxytocic substance 5 days before the successful induction. Case 3 had a total of 75 units of pitocin by intravenous drip 6 days before delivery and 90 units 2 days later. A course of oestrogen was given before the final drip, in which the maximum concentration of pitocin was 35 units per pint (540 ml.) and the total dose 90 units. Case 5 was given a drip with maximum concentration of 55 units per pint (540 ml.) 3 days before delivery and had some "show" early in the morning of the day when the second drip was set up. The abortion was complete 45 minutes after the start of the drip.

Seven of the 18 cases required surgical evacuation of the uterus to complete the process of abortion, but the last 11 cases include only 3 of these, if one excepts Case 18 where the uterus was explored as a matter of policy on account of the hydatidiform mole. Exploration would otherwise not have been carried out for the patient had no excessive vaginal bleeding such as would make one suspect retained products of conception.

In only one case did the blood loss exceed 1 pint (540 ml.) and in the great majority of cases the loss was described as "minimal".

Routine estimation of plasma fibrinogen was not carried out, but no case showed evidence of failure of the clotting mechanism after delivery. Quinn and Harper (1955) refer to the possibility that the use of pitocin may increase the danger of introducing toxic substances of an anti-coagulant nature from the placenta into the maternal circulation. Even with the high doses employed in some of these patients no evidence of such an occurrence appeared.

In 2 cases a concentration of 100 units of pitocin per pint (540 ml.) was employed and one of these patients received a total of 350 units. This patient had fairly severe cutaneous vasoconstriction for a short period during the administration of pitocin, but her blood pressure

remained unaffected. She was the only patient in the series in whom this effect was noted and she herself had no subjective symptoms. Two patients experienced mild frontal headache with the higher concentrations. No other toxic manifestations were noted in any patient. No case showed significant suppression of urinary output.

Two cases are fully described, Cases 17 and 18. The first is a typical case of missed abortion and Case 18 has been included despite the fact that the cause of failure of the pregnancy was hydatidiform mole and not true missed abortion, because it illustrates a further use for this method of treatment.

Case Histories

Case 17

The patient was aged 34 years and this was her fourth pregnancy. In 1953 she had been delivered by forceps of a healthy male child. In 1955 her second pregnancy had resulted in a stillborn male child weighing 8 pounds 4 ounces at 38 weeks. The cause of death was hydrops foetalis, the patient being Rh negative and her husband Rh positive, homozygous genotype CDe/cDE. In 1957 her third pregnancy had ended at 24 weeks in missed abortion. Delivery was induced by pitocin drip and the macerated foetus which weighed 575 g. showed evidence of haemolytic disease.

Her last menstrual period had begun on 19th October, 1957. She felt movements at the 18th week and at this time antibody titres were saline: nil; albumin: 1/64. On 11th April, 1958 when she was 24-weeks pregnant movements ceased, though the foetal heart was still definitely audible the following day. Shortly after this the patient noted marked swelling of her abdomen and legs, and, although she said both were diminishing when she was seen on 21st April, hydramnios and pitting oedema of the ankles were both present. Just about the time the swelling started to diminish she noted a generalized itch, but no visible rash appeared. There was, however, no marked gain in weight and thus the full picture of the maternal syndrome in impending foetal death *in utero* due to iso-immunization as described by Goodlin (1957) was not present.

The patient was admitted to hospital on 28th April, 17 days after she had last felt foetal movements. An X-ray of the abdomen on the day of admission showed hydramnios but no evidence of intra-uterine death. Plasma fibrinogen at that time was 740 mg. per 100 ml.

Despite the negative radiological findings, both obstetricians and patient were so convinced that intra-uterine death had taken place that it was decided to induce abortion with a pitocin drip. This was set up at 9.50 a.m. on 3rd May, 1958 and progress was as follows:

9.50 a.m.	Drip set up, concentration 20 units per pint, rate 25 drops per minute.
12.50 p.m.	The uterus was observed to be contracting with moderate strength every 3 to 4 minutes and the drip rate was increased to 34 drops per minute.
3.15 p.m.	Rate increased to 40 drops per minute.
5.20 p.m.	Concentration of pitocin increased to 40 units per pint at 25 drops per minute.
5.45 p.m.	Frequent painful contractions were now occurring, so the patient was given pethidine 100 mg. and the rate of flow decreased to 20 drops per minute.
7.10 p.m.	Abortion of a severely macerated foetus weighing 427 g.
7.23 p.m.	The placenta was expelled.
8.00 p.m.	There had been minimal vaginal bleeding. The drip was discontinued. The foetus showed evidence of haemolytic disease.

The patient made an uneventful convalescence with rapidly diminishing lochia and was discharged home on 9th May, 1958.

Case 18

The patient was aged 29 years and para-2, having had uneventful pregnancies ending in delivery at term of healthy babies in 1952 and 1956. Her last menstrual period had begun on 30th June, 1957. On 20th September, 1957 she had been booked for home confinement by her own general practitioner and was seen by him at two-weekly intervals on account of a persistent hypertension in the region of 140/100. On 22nd November she had slight painless bleeding which lasted one week at the end of which the uterus was noted to be of a size consistent with a 20-weeks pregnancy. Early in January, 1958 she developed brown vaginal discharge and was referred to hospital by her doctor for opinion because the uterus was no longer palpable per abdomen.

When she was seen on 14th January the uterus appeared on bimanual examination to be the size of a 10-weeks pregnancy. A Hogben test was positive.

She was seen again on 1st February, by which time the uterus was thought to have enlarged to the size of a 12-weeks pregnancy. Slight further increase in size was observed by 15th February and a quantitative Hogben test gave the following results:

Undiluted	—	positive
1/10 dilution	—	negative
1/100 dilution	—	negative

The patient was therefore returned to the care of her own doctor as an apparently normal pregnancy, but she was once more referred to hospital on 28th March because the uterus was again smaller.

She was admitted to hospital on 5th April. On examination the fundus of the uterus could be felt 3-fingers breadths above the symphysis pubis and a further quantitative Hogben test gave the same results as above.

A diagnosis of missed abortion probably due to hydatidiform mole was made and it was decided to treat her with pitocin drip. This was set up at 8.45 a.m. on 14th April, 1958 and progress was as follows:

8.45 a.m.	Drip set up, concentration 20 units per pint, rate 20 drops per minute.
9.7 a.m.	Drip rate increased to 40 drops per minute.
9.45 a.m.	Drip rate increased to 60 drops per minute.
10.45 a.m.	Concentration of solution increased to 40 units per pint at rate of 40 drops per minute.
11.55 a.m.	Rate increased to 80 drops per minute.
12.40 p.m.	The patient was feeling slight "pains" and there was a little bleeding *per vaginam*. The concentration of pitocin was increased to 80 units per pint at 30 drops per minute.
3.0 p.m.	"Pains" were more severe and the patient was experiencing slight frontal headache. She was given pethidine 100 mg.
4.30 p.m.	The contractions were becoming even more painful and the patient was given morphine gr. ¼ (16 mg.).
5.5 p.m.	Hydatidiform mole passed.
5.20 p.m.	There had been minimal vaginal bleeding, so the pitocin drip was discontinued.

The mole appeared to be for the most part dead, but it was deemed advisable to carry out curettage of the uterus after allowing some time for involution to commence. Accordingly the uterus was curetted under general anaesthesia on 21st April. Minimal scrapings were obtained.

Hogben tests after delivery of the mole gave the following results:

	Undiluted	1/10	1/100
15th April ..	Positive	Negative	Negative
16th April ..	Positive	Negative	Negative
17th April ..	Positive	Weak positive	Negative
18th April ..	Negative	Negative	Negative
19th April ..	Negative	Negative	Negative
20th April ..	Negative	Negative	Negative

The patient was allowed to go home on 24th April, 1958.

Summary

The available methods of managing missed abortion are discussed.

The treatment of 18 cases of missed abortion with high concentration pitocin intravenous drip is described and it is claimed that this technique offers a reliable, rapid and safe method of managing missed abortion.

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THE EXCRETION OF CHORIONIC GONADOTROPHIN BY WOMEN WITH CHORIOADENOMA AND CHORIOCARCINOMA

BY

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INTRODUCTION

CHORIONIC gonadotrophin (C.G.) is excreted in large amounts in normal pregnancy, and by women with hydatidiform mole, chorioadenoma destruens and choriocarcinoma. The value of estimating quantitatively the amount of C.G. excreted lies in the fact that larger amounts of the hormone are usually produced by women with tumours, especially during the last trimester of pregnancy. Although the amounts of C.G. excreted by pregnant women, and those with tumours of the chorion, are extremely variable and the range of values overlaps, this does not prevent the results of the biological tests from being important aids when they are used in conjunction with clinical and pathological findings.

The information available about the excretion of C.G. by women with "chorionepithelioma" is limited to a few isolated observations. The results obtained have usually been expressed in "animal units", thus preventing the comparison of data collected in different laboratories. The most informative work on the excretion of C.G. by women with "chorionepithelioma" is that of Hamburger (1944) and Hamburger and Terkildsen (1948). Although these authors expressed the results of their investigations in International Units of C.G. they did not distinguish between chorioadenoma and choriocarcinoma but included both in the term chorionepithelioma (Hamburger, 1955).

The object of the present investigation is to provide information about the excretion of C.G. by women with chorioadenoma and choriocarcinoma before and after hysterectomy. Some information has been obtained about the effect of X-rays and hormonal treatment upon the excretion of C.G. and upon the progress of the disease.

MATERIALS AND METHODS

First morning specimens of urine were obtained from 11 women with chorioadenoma and 18 women with choriocarcinoma. In most cases urines were collected before and after hysterectomy. The concentration of C.G. in each specimen was estimated by one of two methods: the Hogben dilution test (Hobson, 1952) and bio-assays using male *Xenopus laevis* (Hobson and Landgrebe, 1954). Except for Case CC 11, from which 24-hour collections of urine were available, the results of the bio-assays were expressed in I.U.C.G. per litre of urine.

RESULTS

Group 1. Choriocarcinoma

There were 18 women in this group between the ages of 11 and 49 years for whom a diagnosis of choriocarcinoma was made. Metastases were present in all the women, and, with the exception of Case CC 6, all were hysterectomized.

Choriocarcinoma developed in 4 women after a normal delivery of a living child, in 1 woman after a miscarriage in the second trimester of pregnancy, in 1 woman after a missed abortion, in 2 women after an extra-uterine pregnancy, in 2 women after periods of amenorrhoea, and in 7 women after a previous hydatidiform mole. A primary choriocarcinoma of the right ovary was found in a pre-pubertal girl. At the present

time, only 3 women in the group remain alive.

Quantitative or semi-quantitative estimations of C.G. were made on 47 specimens of urine obtained before hysterectomy, and on 204 obtained post-operatively. The results of these bio-assays and other information are given in Table I.

A comparison of the maximum amounts of C.G. excreted before and after hysterectomy shows that only 2 women, CC 1 and CC 4, excreted less C.G. after hysterectomy.

Hogben tests done before hysterectomy were negative in 3 cases. In the first case, CC 11, a single test was done 10 days after the removal of an ectopic pregnancy (i.e., 3 weeks before hysterectomy) and it was negative. In the second case, CC 14, 3 Hogben tests were done. The first was made immediately after the removal of a hydatidiform mole and the other tests were done 1 and 5 months later. In the third case, CC 15, the patient had a mole removed in September, 1951. This woman was followed up until November, 1954; during this period the Hogben tests were negative and when seen in October, 1955 she was thought to be 2-months pregnant. When she was re-examined in January, 1956 there was no clinical evidence of pregnancy. Amenorrhoea persisted for a further 2 months and was then followed by bleeding for 5 weeks. Two specimens of urine collected on 13th and 14th April, 1956 were found to contain 987,000 and 1,220,000 I.U.C.G. per litre respectively. A large choriocarcinoma in the uterus and a secondary growth in the posterior wall of the vagina were found when a panhysterectomy was done on 14th April. X-irradiation was given for lung metastases. The woman died 4 weeks after the operation.

Negative Hogben tests were obtained from 5 women after hysterectomy and in one of them, CC 1, the tests remained negative. The case histories of 3 of these women are detailed in the following section.

Case History No. CC 1

A girl aged 11, had a teratomatous choriocarcinoma of the right ovary removed in September, 1953. At the same time a nodule from the left ovary was removed which showed features of an arrhenoblastoma. A Hogben test done 3 days post-operatively was positive in a dilution of 1 in 100, and negative in the 1 in 200 dilution. A bio-assay on the same specimen showed that the amount of C.G. per litre of urine was 321,300 I.U. A test done 13 days post-operatively was negative and all tests done since October, 1953 have been negative. In October, 1955 a total hysterectomy was performed as there was a large tumour of the left ovary remnant. Examination of the excised uterus showed a choriocarcinoma. This girl is still alive and well 4 years after the removal of the first choriocarcinoma.

Case History No. CC 4

This woman had a normal delivery in August, 1954. Hogben tests done post-partum were positive and 2 months after parturition the woman was excreting between 300,000 and 600,000 I.U.C.G. per litre. A hysterectomy was done in October, 1954 and the Hogben tests were persistently positive until January, 1955. During the following 10 months the Hogben test was negative. In November the test again became positive. Monthly tests done in 1956 and 1957 have all been negative and this woman is alive and well.

Case History No. CC 18

This woman spontaneously aborted a hydatidiform mole 22 weeks after her last menstrual period. Curettings taken shortly after were suggestive of chorioadenoma and a hysterectomy was done in July, 1952. The first Hogben test for this patient was done 12 days post-operatively and was negative. This woman failed to report for follow-up and was not seen again until January, 1953 when she was admitted to hospital with severe abdominal pains. Bio-assays done on the 9th, 12th, 20th and 26th January showed that this patient was excreting 624,000, 312,000, 562,000 and 1,150,000 I.U.C.G. per litre of urine. A 24-hour specimen of urine collected on 23rd January contained 894,000 I.U.C.G. This woman died on 27th January and at autopsy widespread metastases were found in both lungs, the liver and in some bones.

Effect of Therapy Upon the Excretion of C.G.

Some information was obtained about the effect of X-rays or hormone therapy upon the excretion of C.G. by 4 women with a choriocarcinoma. Thirty-nine urines, 18 from patient CC 10, 9 from patient CC 11, 7 from patient CC 17, and 5 from patient CC 3, were assayed before, during and after treatment.

Case History No. CC 10

This woman had a ruptured ectopic pregnancy in December, 1952. A sub-total hysterectomy and bilateral salpingo-oöphorectomy were done on 11th December. The woman was re-admitted to hospital in March, 1953 with a mass in the pelvis and an intestinal obstruction. The diagnosis was choriocarcinoma. The amount of C.G. excreted by the woman 106 days after hysterectomy and 6 days before X-irradiation therapy was

TABLE I

C.G. Excretion by 18 Women with Choriocarcinoma. Figures in Parenthesis Refer to the Time at Which the Estimation of C.G. was Made

Patient Ref. No.	Age (years)	Previous Condition	I.U.C.G. Per Litre. Maximum Level		Time Patient Survived after Hysterectomy
			Before Hysterectomy	After Hysterectomy	
CC 1 ..	11	Ovarian choriocarcinoma	321,300 (25 months)	Hogben tests negative	2 years*
CC 2 ..	46	Amenorrhoea	No test	>450,000<600,000 (5 weeks)	6 weeks
CC 3 ..	25	Amenorrhoea	870,000 (1 week)	2,965,000 (2 weeks)	3 weeks
CC 4 ..	21	Normal delivery	>300,000<600,000 (2 weeks)	>300,000<450,000 (2 weeks)	2½ years*
CC 5 ..	25	Normal delivery	3,173,000 (1 day)	No test	1 day
CC 6 ..	28	Normal delivery	>30,000<300,000 (20 weeks)	Not hysterectomized	Dead
CC 7 ..	30	Normal delivery	>30,000<300,000 (1 week)	>30,000<300,000 (10 weeks)	5 months
CC 8 ..	27	Miscarriage	No test	>30,000 <45,000 (8 weeks)	8 weeks
CC 9 ..	35	Missed abortion	No test	>30,000<300,000 (9 weeks)	11 weeks
CC 10 ..	29	Ectopic pregnancy	No test	1,330,000 (20 weeks)	7 months
CC 11 ..	33	Ectopic pregnancy	Hogben test negative (3 weeks)	7,340 (25 weeks)†	3 years*
CC 12 ..	24	Hydatidiform mole	No test	295,600 (8 months)	13 months
CC 13 ..	26	Hydatidiform mole	>3,000 <30,000 (4 weeks)	>30,000<300,000 (3 weeks)	7 weeks
CC 14 ..	32	Hydatidiform mole	Hogben tests negative (16, 13 and 1 week)	>3,000 <30,000 (10 weeks)	12 weeks
CC 15 ..	33	Hydatidiform mole	Hogben tests negative	1,220,000 (3 weeks)	4 weeks
CC 16 ..	35	Hydatidiform mole	No test	>30,000<300,000 (16 weeks)	25 weeks
CC 17 ..	37	Hydatidiform mole	3,200 (1 week)	>30,000<300,000 (4 weeks)	14 months
CC 18 ..	49	Hydatidiform mole	No test	1,150,000 (30 weeks)	8 months

* Still alive. † Per 24-hour specimen.

TABLE II

C.G. Excretion by 11 Women with Chorioadenoma. Figures in Parenthesis Refer to the Time at Which the Estimation of C.G. was Made

Patient Ref. No.	Age (years)	Previous Condition	I.U.C.G. Per Litre		Date of Hysterectomy	Time at Which Hogben Test was Negative
			Maximum Level Before Hysterectomy	Maximum Level After Hysterectomy		
CA 1 ..	22	Hydatidiform mole	No test	276,840 (1 day)	August, 1951	7 weeks
CA 2 ..	23	Hydatidiform mole	No test	Hogben test negative (2 weeks)	April, 1950	2 weeks
CA 3 ..	23	Hydatidiform mole	>30,000 <300,000 (9 weeks)	Hogben test negative (2 weeks)	November, 1953	2 weeks
CA 4 ..	25	Hydatidiform mole	2,987 (1 week)	1,575 (2 days)	April, 1953	2 days
CA 5 ..	30	Hydatidiform mole	>600,000 <900,000 (11 days)	Hogben test negative (12 days)	June, 1954	12 days
CA 6 ..	32	Hydatidiform mole	>1,200,000<1,500,000 (10 weeks)	Hogben test negative (12 days)	May, 1954	12 days
CA 7 ..	32	Hydatidiform mole	No test	>3,000<30,000 (3 days)	October, 1955	15 days
CA 8 ..	35	Hydatidiform mole	>30,000 <300,000 (2 weeks)	Hogben test negative (20 days)	April, 1956	20 days
CA 9 ..	36	Hydatidiform mole	>30,000 <300,000 (5 weeks)	24,810 (11 days)	May, 1956	4 weeks
CA 10 ..	37	Hydatidiform mole	>300,000 <450,000 (5 weeks)	3,750 (15 days)	January, 1956	22 days
CA 11 ..	46	Hydatidiform mole	>3,000 <30,000 (1 week)	Hogben test negative (3 weeks)	October, 1952	3 weeks

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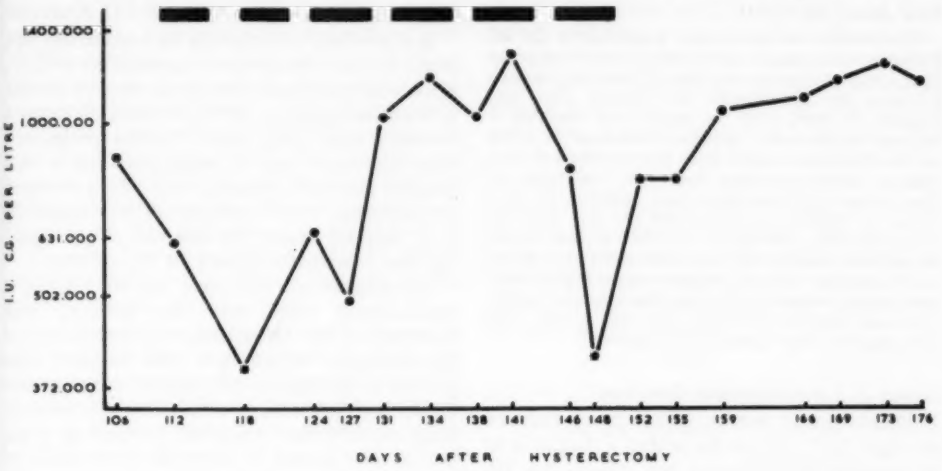

FIG. 1

C.G. excretion by a woman, Case CC 10, with a chorio-carcinoma before, during and after X-irradiation. Solid rectangles show when treatment was given.

874,000 I.U. per litre. Three weeks after the start of the treatment the level of C.G. in the urine was above pre-treatment level and continued to rise during the next two courses of treatment. The largest amount of C.G. excreted was on the 141st day after hysterectomy, 1,330,000 I.U. per litre. This was followed by a temporary drop in the amount excreted until the next and last course of therapy when the pre-treatment level was again passed (Fig. 1). This patient died 7 months after hysterectomy.

Case History No. CC 17

This woman was found to have a choriocarcinoma of the uterus one year after the abortion of a hydatidiform mole. Assays done after the expulsion of the mole and until hysterectomy a year later, showed a fairly constant urinary level of C.G. between 1,600 and 3,200 I.U. per litre. During this time the patient was apparently free from metastases. Three months post-operatively the patient was excreting between 3,000 and 6,000 I.U. per litre and during the next 4 weeks the level of C.G. in the urine rose to 30,000 I.U. per litre. An X-ray revealed multiple secondary deposits in the lungs. Deep X-ray therapy was given during the next three months and the Hogben test was negative after this treatment. At the same time the chest metastases were reported to have cleared. A Hogben test done a month later was positive with undiluted urine, though negative in a dilution of 1 in 10. During the next month the amount of C.G. excreted fluctuated between 5,000 and 10,000 I.U. per litre and rose in the following month to 30,000 I.U. per litre. An X-ray of the chest showed that the metastases had reappeared. Following a second course of treatment the amount of C.G. excreted dropped to between 3,000 and 6,000 I.U. per litre. The patient died 14 months after hysterectomy, and at post mortem secondary deposits of choriocarcinoma were found in the brain, lungs, kidneys and spleen.

Case History No. CC 3

This woman had two previous miscarriages and was admitted to hospital with a uterus the size of a 3-months pregnancy, following an amenorrhoea of 5 months duration. On the day of admission the patient had a haemorrhage from the vagina, but no products of conception were passed. A provisional diagnosis of missed abortion was made. Bleeding from the vagina occurred 5 days later and continued for 4 days. The uterus was curetted and some necrotic material was obtained which appeared to be aberrant trophoblastic tissue. A chest X-ray revealed shadows which were suggestive of metastases. A specimen of urine, collected 7 days before the operation, was assayed and found to contain 870,000 I.U.C.G. per litre. A total hysterectomy was done and necrotic ulceration at the fundus of the uterus with secondary tumours in both ovaries was found. Following hysterectomy the patient was treated with 300 mg. methyl testosterone per week. Specimens of urine, collected 2, 11 and 14 days post-operatively, contained 900,000, 1,500,000 and 2,965,000 I.U.C.G. per litre respectively. This patient died 3 weeks after hysterectomy.

Case History No. CC 11

This woman had an ectopic pregnancy in the left Fallopian tube removed in October, 1954. Four weeks later a panhysterectomy was done. During the 5 months following the hysterectomy the Hogben tests were negative. In May, 1955 the patient was admitted to hospital with secondary growths in the lungs for which she received X-irradiation. A 24-hour specimen of urine collected before treatment contained 7,340 I.U.C.G. Twenty-four hour specimens were collected during a course of treatment, on 17th, 22nd and 25th June and contained 4,095, 3,090 and 2,750 I.U.C.G. respectively. During the treatment the lung metastases were observed to be enlarging. The first Hogben test made after treatment was in November, 1955, and was negative. Hogben tests done between November, 1955 and August, 1956 were negative. This woman is alive and well.

Group 2. Chorioadenoma Destruens

There were 11 women in this group between the ages of 22 and 46 for whom a diagnosis of chorioadenoma destruens was made. All the women in the group were hysterectomized and are still living. Quantitative or semi-quantitative estimations of C.G. were made on 86 specimens of urine. Twenty-two of these were collected before hysterectomy and 64 collected in the post-operative period. The results obtained with the biological tests and other information are shown in Table II.

In this group of women post-operative convalescence was not complicated by secondary growths. The excretion of C.G. after hysterectomy was not excessive and the biological tests, with one exception, became negative within 4 weeks after operation. The exception is Case CA 1, for whom we did the first test 7 weeks after hysterectomy. This was negative.

Anaplasia of Chorionic Tissue and C.G. Excretion

In a previous investigation no correlation was found to exist between the concentration of C.G. in hydatidiform moles, and the amounts excreted in the urine (Hobson, 1955). A choriocarcinoma develops more often after a molar pregnancy than any other type of pregnancy, and it was thought that a relationship might exist between the pathology of the mole tissue, the amount of C.G. excreted before the removal of the mole, and the subsequent history of the patient.

Histological sections were obtained from 4 hydatidiform moles and this material was examined in the Department of Obstetrics and Gynaecology, Edinburgh. The moles were graded according to the degree of anaplasia exhibited. The amount of C.G. in the urine of these women was estimated at varying times before the removal of the mole. The results of these 2 independent investigations are shown in Table III.

Patient A 86 was hysterectomized but the other 3 women had normal menstrual cycles within 3 to 5 months of their mole being removed. A follow-up 5 years later showed that all these women were alive and well. Two women still have normal menstrual cycles and one woman has now reached the menopause.

Discussion

Before hysterectomy the amounts of C.G. excreted by women who had a choriocarcinoma or chorioadenoma were similar (Tables I and II). A distinction between the two conditions cannot

Table III

C.G. Excretion by 4 Women with Molar Pregnancies and the Degree of Anaplasia of the Mole

Patient's Reference No.	Test Done Before Removal of Mole	I.U.C.G. per Litre	Pathologist's Report
A 99	8 days 4 days 1 day	3,250,000 2,750,000 3,500,000	Active regular cells.
A 89	7 days	>300,000<450,000	More activity and more anaplasia.
B 71	3 days	>30,000<45,000	Ordinary hydatid villi but one area of greater activity and anaplasia on decidual plate.
A 86	9 days	3,400	Very anaplastic and patient should be carefully followed up.

be made on the results of the pre-operative assays alone. Post-operatively the women with choriocarcinoma continued to excrete large quantities of C.G. which was presumably produced by metastases. After hysterectomy the urine from women with chorioadenoma contained little or no C.G. The Hogben test may be expected to become negative within 4 weeks after the removal of a chorioadenoma. Because of this difference, the estimation of C.G. after hysterectomy is a valuable aid to diagnosis and also provides a measure of the effectiveness of any treatment.

There are numerous reports, both favourable and unfavourable, in the literature about the capacity of oestrogens and androgens to suppress the excretion of C.G. and the metastases which produce the hormone. If the lowered excretion of C.G. is a reflection of the effectiveness of X-irradiation and other forms of therapy upon choriocarcinoma it would appear from the results of the present investigation that the response of choriocarcinoma to treatment is not great. In those cases where regression of metastases does occur it is usually of a temporary nature. Following the removal of the primary choriocarcinoma, 6 women in the present series received radiological treatment for metastases. Five of these women died, and in only one case, CC 11, was the reduction of metastases and the suppression of C.G. excretion followed by recovery. One woman, CC 3, was treated with 300 mg. of methyl testosterone weekly after hysterectomy. During the treatment and until the death of the patient the amount of C.G. excreted continued to rise. The other 11 in the choriocarcinoma group received no post-operative therapy; 2 of these women, CC 1 and CC 4, are still alive. The 11 women who had a chorioadenoma, and no post-operative therapy, are all living 2 to 8 years after hysterectomy. It is difficult to estimate the value of the various forms of therapy because they are usually used in combination with surgery, and in a very few cases the tumour is said to regress spontaneously (Smalbraak, 1957), but it seems that the chances of a patient with choriocarcinoma recovering are extremely small.

Attempts have been made to find out by histological examination whether chorionic tissue will become malignant. Novak and Seah (1954), and Hertig and Mansell (1956) believe, however, that histological findings are not of much value in estimating the degree of malignancy. Estimation of the C.G. content of urine from patients who have a hydatidiform mole suggests that, where the amount of C.G. excreted is low, the tissue may be highly anaplastic (Table III) but it would be unwise to draw any general conclusion from 4 cases, especially when women with highly malignant choriocarcinoma may excrete either large quantities, or occasionally no measurable amount, of the hormone.

Summary

(1) Data are presented on the excretion of C.G. before and after hysterectomy by 11 women with chorioadenoma destruens and 18 women with choriocarcinoma.

(2) Before hysterectomy the amounts of C.G. excreted by both groups of women is similar. Post-operatively the women with choriocarcinoma continued to excrete large quantities of C.G. up to the time of death. In 3 women who are still alive the Hogben tests finally became negative. The urine from women with a chorioadenoma contained no measurable amount of C.G. 4 weeks after hysterectomy.

(3) The effectiveness of various forms of treatment upon chorioadenoma and choriocarcinoma is considered.

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PRE-MENOPAUSAL CYSTIC HYPERPLASIA AND ENDOMETRIAL CARCINOMA

BY

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CYSTIC glandular hyperplasia of the endometrium is in most cases a frankly benign lesion, both clinically and histologically. In some cases, however, the degree of epithelial proliferative activity is so extreme that the resemblance to adenocarcinoma is very striking and indeed in some instances there may be considerable doubt as to whether the lesion is in fact malignant. This has led to the opinion that cystic glandular hyperplasia is a precancerous condition. Since hyperplasia of the endometrium is closely related to oestrogenic activity it has been inferred that endometrial carcinoma is the result of long-continued action of the oestrogen.

The apparently high incidence of endometrial carcinoma in cases of granulosa cell and thecoma tumours of the ovary has given support to the view that oestrogenic activity, endometrial hyperplasia and carcinoma are closely related. From a study of the genital tract in post-menopausal women suffering from endometrial carcinoma I (McBride, 1955) came to the conclusion that there was no evidence of a continuing abnormal oestrogen activity. But it seemed that this did not rule out the possibility that abnormal oestrogen influence might have been present some years before the development or discovery of the carcinoma. Such an influence could conceivably be manifested by an episode of cystic glandular hyperplasia of the endometrium during the later years of childbearing life or actually at the time of the menopause.

Further support for this idea is provided by frequent association of "retrogressive hyperplasia" or cystic atrophy and carcinoma of the endometrium reported by Novak and Richardson (1941) and McBride (1955). The former authors considered that "retrogressive hyperplasia" was an endometrial pattern found in the post-menopausal woman who had suffered from active hyperplasia at the time of the menopause. If this were the correct explanation of the development of an endometrium with numerous cystic glands then a follow-up of cases of menopausal menorrhagia associated with cystic glandular hyperplasia should reveal a considerable proportion of cases of endometrial carcinoma.

It has been shown by Hertig and Somers (1949) who studied prior biopsies in cases of endometrial carcinoma that many of these patients had previously had endometrial hyperplasia, commonly of an adenomatous pattern. It therefore seems important to determine if endometrial hyperplasia is a frequent precursor of carcinoma. The problem has an important clinical bearing. Although hysterectomy is frequently performed in cases of excessive bleeding at the menopause associated with endometrial hyperplasia, the induction of an artificial menopause by X-rays or radium is still common practice. If hyperplasia were frequently followed by carcinoma this would be a powerful argument in favour of the surgical treatment of this condition.

The literature in connexion with this subject is very involved and there are few straightforward follow-up studies of cases of cystic glandular hyperplasia apart from that by Hintz (1929). One of the first lines of approach was based on the impression that patients who had

a late menopause were prone to develop endometrial carcinoma (Randall, 1945) although there was no evidence that such patients were more liable to have cystic glandular hyperplasia than women who have their menopause in the early forties. It was next suggested that patients who suffer from abnormal bleeding at the time of the menopause are likely candidates for the development of carcinoma of the corpus (Hunter *et al.*, 1954). In this connexion some authors appear to have assumed that abnormal bleeding at the time of the menopause is invariably associated with endometrial hyperplasia. The position was further complicated by the frequent use of deep X-rays or radium for the induction of an artificial menopause in such cases. Soon reports were forthcoming of the frequent development of uterine malignancy in patients who had previously had such therapy and many follow-up studies are focussed on this aspect of the problem (Norris and Behney, 1936; Costolow, 1941; Corscaden, Fertig and Gusberg, 1946; Thornton, Nokes and Brown, 1951; Montgomery, Long and Hoffman, 1952; Turnbull, 1956). In many instances little attention was paid to the endometrial pattern at the time of curettage and, particularly in the United States, there were instances of patients suffering from dysfunctional bleeding or menorrhagia associated with fibroids where a diagnostic curettage had not been performed.

For these reasons it seemed to the present writer important that a follow-up study should be carried out dealing only with patients in whom a diagnosis of cystic glandular hyperplasia of the endometrium had been made. In fact a proportion of the patients studied by me did have an artificial menopause induced by deep X-rays or radium. In order to ensure that uniform criteria for the diagnosis of endometrial hyperplasia were adopted all the curettings or uteri were examined personally by me. When the histological specimens were being assessed I found that there were degrees of severity of the hyperplasia. There was the characteristic picture of cystic glandular hyperplasia—well described by Novak—sometimes with areas showing an adenomatous pattern. In other instances the degree of hyperplasia was not so pronounced. Either the condition was localized in the form of a polyp, or secretory changes were present in an adjacent piece of endometrium or a proliferative endometrium showed areas with cystic gland aggregations.

Two points were obvious before the actual follow-up began. First, cystic glandular hyperplasia occurring at the time of the menopause is for the most part a disease of parous women and often of patients who have had a considerable number of pregnancies. About 18 per cent of all patients were nulliparous; about half of these were unmarried, and some were cases of puberty bleeding. The condition was also diagnosed in the investigation of infertility. Some of the unmarried patients subsequently married and later had families. Endometrial carcinoma on the other hand occurs more among nulliparous women or patients of low parity although there are many exceptions. Taylor and Becker (1947) found that 31·5 per cent of their patients with endometrial carcinoma were nulliparous and Hawksworth (1950) gives the figure of 40 per cent. These figures refer mostly to women who have already passed the child-bearing period.

There are relatively few women still menstruating after the age of 50 years. Over 60 per cent of all patients with endometrial hyperplasia were aged between 40 and 50 years and only 12 per cent were over 50 years. When abnormal bleeding was complained of by patients over 50 years old there was frequently a history of amenorrhoea for a year suggesting that these cases came under the heading of post-menopausal bleeding. They are therefore not included in the present study.

I have been able to trace and follow up 544 patients, and for purposes of the present investigation have divided them into five groups.

A. Patients in whom no further abnormal bleeding occurred.

B. Cases where the endometrium was subsequently available for examination.

C. A small group of patients who continued to have irregular bleeding.

D. Deaths.

E. Two patients who developed endometrial carcinoma.

These categories will now be considered in detail. In the groups containing a large number of patients the cases were further classified into sub-groups according to the age of the patient.

A. Patients in Whom No Further Abnormal Bleeding Occurred

There were 419 such cases and the follow-up extended over periods of up to 24 years.

(1) In 81 cases the patient was under 40 years at the time of curettage where endometrial hyperplasia was present. In 52 patients the full picture of cystic glandular hyperplasia was present. Not all of these patients were suffering from abnormal bleeding; a few instances came to light at curettage in the investigation of infertility. Seven patients were treated by a menopausal dose of deep X-rays and a similar number had a menopause induced by radium. Curettage was the only surgical procedure adopted in the others although this was followed in some instances by hormone therapy. Most of the patients have since experienced a natural menopause and of the youngest age group 5 patients have subsequently had one or more pregnancies.

(2) The largest numerical sub-group was of patients aged between 40 and 50 years—a total of 308. Ninety-two cases were of the type I have called localized hyperplasia and 216 were examples of generalized cystic glandular hyperplasia. In a few of these an adenomatous pattern was present. A menopause was induced by X-rays in 100 instances and by radium in a further 33. The menopause occurred naturally in the other cases often relatively soon after the curettage and has been completed in all the patients in this category. Any subsequent menstrual irregularity was of a minor and temporary nature and there was no post-menopausal bleeding. The great majority of the patients have been followed for more than 10 years and so are many years beyond the menopause.

(3) There was a relatively small proportion of patients over the age of 50 years showing cystic glandular hyperplasia and not past the menopause. Thirty patients were followed for from 5–24 years without the recurrence of abnormal bleeding. Fifteen of these women were treated by a menopausal dose of deep X-rays and twice a menopause was induced by radium.

TABLE I

Follow-Up of Patients with No Further Abnormal Bleeding
81 Patients. Age Under 40 Years

Duration of follow-up	0–4 years	5–9 years	10–14 years	15–19 years	20–24 years
Cystic glandular hyperplasia	—	7	16	19	10
Localized hyperplasia	—	4	9	12	4
Total	—	11	25	31	14

7 cases treated by a menopausal dose of deep X-rays.
7 cases treated by radium.

TABLE II

Follow-Up of Patients with No Further Abnormal Bleeding
308 Patients. Age 40–45 Years

Duration of follow-up	0–4 years	5–9 years	10–14 years	15–19 years	20–24 years
Cystic glandular hyperplasia	1	32	81	75	27
Localized hyperplasia	1	11	48	24	8
Total	2	43	129	99	35

180 cases treated by a menopausal dose of deep X-rays.
33 cases treated by radium.

TABLE III

Follow-Up of Patients with No Further Abnormal Bleeding
30 Patients. Age Over 50 Years

Duration of follow-up	0–4 years	5–9 years	10–14 years	15–19 years	20–24 years
Cystic glandular hyperplasia	—	—	10	3	1
Localized hyperplasia	—	2	8	3	3
Total	—	2	18	6	4

13 cases treated by a menopausal dose of deep X-rays.
2 cases treated by radium.

These findings are illustrated in Tables I, II and III.

There is a possible criticism of these figures. Rarely, at a routine curettage prior to a pelvic floor repair in a patient not suffering from bleeding, an unsuspected endometrial carcinoma is found. But this is most unusual and by and large patients past the menopause do ultimately present with a history of vaginal bleeding. The length of the follow-up in the present series renders it unlikely that carcinoma developed in the cases under review.

B. Cases Where the Endometrium was Subsequently Available for Examination

More definite information is available in another group of cases numbering 78 in which it was possible to examine the endometrium some years after the original diagnosis of endometrial hyperplasia was made. In a number of instances further operation was necessary because of a recurrence of abnormal bleeding but in 10 cases the patient was suffering from prolapse and the endometrium was available from a routine curettage or the uterus was removed when vaginal hysterectomy was the treatment adopted.

1. SUB-GROUP AGED UNDER 40 YEARS

Thirty-four of the patients were under 40 years of age at the time of the original curettage and a further opportunity to examine the endometrium occurred from 4 months to 15 years later. In 3 instances the patient was curetted on a third occasion.

The findings are shown in Table IV.

Follow-up 0–4 Years. There were 15 patients whose subsequent curettage took place less than 5 years after the original diagnosis of hyperplasia was made. In 9 instances hyperplasia was also encountered at the time of the second curettage. The remaining 6 endometriums showed a normal endometrial pattern on the second occasion. One of the 9 patients where hyperplasia was noted required to be curetted a third time and a normal secretory pattern was noted, and 2 others later became pregnant, so that in all 9 of the patients subsequently showed a reversal

TABLE IV

Follow-Up of Patients in Cases Where the Endometrium was Subsequently Available for Examination
34 Patients (36 Specimens). Age Under 40 Years

Interval in years	0–4 years	5–9 years	10–14 years	15–19 years
Hyperplasia	9	3	1	1
Proliferative phase	1	–	–	–
Secretory phase	2	4	1	1
Atrophic endometrium	3	1	4	3
Decidua	–	–	1	–
Unknown	–	–	1	–
Total	15	8	8	5

to a normal endometrial pattern. Moreover, 2 patients who had hyperplasia three and four and a half years after a similar diagnosis had a normal menopause 14 and 17 years later with no further complaint of abnormal bleeding.

Follow-up 5–9 Years. There were 8 patients in this group. Three patients showed a recurrence of endometrial hyperplasia and in 5 instances the endometrium obtained at the second curettage was of a normal pattern. Two of the former category were treated by hysterectomy and the third patient subsequently had a natural menopause. One of the patients whose endometrium showed a secretory pattern became pregnant two years later.

Follow-up 10–14 Years. In this group a normal endometrial pattern was noted at the second curettage in 6 cases out of 7. In the case where the histology was unknown the patient was treated by hysterectomy and the endometrium was noted as being thick and haemorrhagic.

Follow-up 15–19 Years. It will be seen that the second curettings showed a normal endometrial pattern in 4 cases out of 5.

In the younger age group therefore a reversion to a normal type of endometrium frequently occurred even after a second curettage had shown a recurrence of endometrial hyperplasia. It was also observed that normal endometrium might be present and indeed pregnancy might supervene between metropathic episodes or after a single curettage where hyperplasia was found to be present. When a considerable number of years had elapsed between the two curettages, atrophy of the endometrium was the usual finding at the second operation. The subsequent finding of a normal or atrophic type of endometrium was noted 23 times in 33 patients. Even where cystic glandular hyperplasia persisted or recurred a natural menopause without further abnormal bleeding sometimes ensued although hysterectomy proved necessary in a few cases.

2. Sub-Group Aged 40–50 Years

There were 41 patients in this age group and the endometrium was subsequently available for examination 44 times. The findings are shown in tabular form in Table V.

Follow-up 0–4 Years. Of the 15 cases where the second operation took place less than five years after the original diagnosis of hyperplasia a normal proliferative or secretory pattern was noted on 5 occasions. In 7 instances the endometrium showed simple or cystic atrophy and there were 3 examples of a recurrence of hyperplasia. In 1 of these, however, the endometrium at a later date was found to be atrophic.

Follow-up 5–9 Years. In this group of 13 patients atrophy of the endometrium occurred 11 times. In a further 2 patients a proliferative type of endometrium was observed and only once was a recurrence of hyperplasia observed.

Follow-up 10–14 Years. There were 8 examples of atrophy of the endometrium and 2 cases of localized hyperplasia in the patients where the second histological specimen was obtained from 10 to 14 years after hyperplasia was first noted.

Follow-up 15–19 Years. All 5 patients in this group showed atrophy of the endometrium.

Thus taking the group as a whole, atrophy was noted in 31 cases out of a total of 41, and this finding was more frequent the longer the

Table V

Follow-Up of Patients in Cases Where the Endometrium was Subsequently Available for Examination 41 Patients (44 Specimens). Age 40–50 Years

Interval in years	0–4 years	5–9 years	10–14 years	15–19 years
Hyperplasia	3	1	–	–
Localized hyperplasia	–	–	2	–
Proliferative phase	2	2	–	–
Secretory phase	3	–	–	–
Atrophic endometrium	6	10	8	4
Senile endometrial polyp	1	1	–	1
Total	15	14	10	5

interval between the two curettages. In one instance atrophy was observed after an intermediate finding of secretory endometrium and once it occurred after a second curettage had revealed cystic glandular hyperplasia. When more than five years had elapsed after the original diagnosis the majority of patients were past the menopause. An artificial menopause by X-rays or radium therapy had been induced in 15 patients. Few of the post-menopausal patients had the second operation because of bleeding. In the majority of cases the patient had developed a prolapse and routine curettage was performed prior to a plastic operation.

A normal functional endometrial pattern was found in 7 instances (6 patients), and hyperplasia recurred 6 times. These findings were for the most part observed when there was a short interval between the two curettages and as has been said in one case atrophy supervened when curettage was performed on a third occasion after a further interval of time.

3. Sub-Group Aged Over 50 Years

There were only 3 patients aged over 50 years where the patient had a second operation. Twice the endometrium was noted to be atrophic $2\frac{1}{2}$ and 8 years later respectively. The other patient required hysterectomy one year later because of continued bleeding associated with endometrial hyperplasia.

C. Patients Who Continued to Have Irregular Bleeding

There is one unsatisfactory group of 6 cases where the patient, though still having irregular bleeding, has not accepted advice to come to hospital for further investigation and treatment. Two of these women are pre-menopausal and the other 4 are passing through the menopause with some irregularity and undue prolongation of the bleeding.

D. Deaths

It was inevitable that in a prolonged follow-up of patients in this age group a number of patients would have died. The number of deaths was 27, the principal causes being cardiac failure or cerebral haemorrhage.

E. Subsequent Development of Carcinoma

Malignancy developed in 14 cases in all but in 12 instances the site of the primary lesion was outwith the uterus. There were 6 cases of carcinoma of the bowel and 2 each of breast, ovary and cerebrum. Endometrial carcinoma followed in the remaining 2 cases.

Discussion

Endometrial carcinoma followed on cystic glandular hyperplasia in 2 cases only, an incidence of roughly 0·4 per cent. This would suggest that although endometrial hyperplasia may be a frequent precursor of carcinoma, malignancy supervenes in only a very small proportion of patients known to have had glandular hyperplasia. This would suggest that some other factor exists which has an important bearing on the development of carcinoma. It is known that the nulliparous, obese, hypertensive woman often suffering from senile diabetes is prone to develop cancer of the corpus. Moreover, a familial or hereditary factor is sometimes noted. These conditions were not present in the 2 cases in the present series.

It is difficult to compare the incidence reported here with other reported findings. Rigo, Scipiades and Vaczy (1950) in a follow-up of 240 cases of hyperplasia found an incidence of 4·2 per cent of development of endometrial cancer. But many of their cases of cystic glandular hyperplasia were first observed in the post-menopausal era and Novak has suggested that hyperplasia at this time of life is more likely to be followed by malignancy than hyperplasia occurring during the reproductive life or at the time of the menopause. In other papers the sequence of endometrial hyperplasia and carcinoma is commented upon but the total number of cases of endometrial hyperplasia under investigation is not given. It is not possible in these circumstances to work out the percentage incidence.

The fact that carcinoma develops in patients who have had endometrial hyperplasia should not be allowed to obscure the fact that carcinoma may develop in a woman whose endometrium at a previous curettage had been found to be normal or even atrophic. Smith and Bowden

(1948) found that, of 10 cases of endometrial carcinoma where there had been a prior biopsy, most of the original histological specimens had been labelled chronic endometritis and one, a frozen section, showed a menstrual endometrium. When they reviewed the histology of the other cases they found one instance of cystic hyperplasia and all the rest had essentially normal endometrium in various stages of the menstrual cycle. The endometrium showed a secretory pattern in 4 cases and a proliferative phase in 2. Hertig and Somers (1949), on the other hand, also in a retrospective study of cases of endometrial carcinoma, found endometrial polyps, hyperplasia or anaplasia in all but 12 out of 32 cases. While this suggests that hyperplasia is a frequent precursor it gives no idea of the incidence of carcinoma in cases of hyperplasia. Montgomery, Long and Hoffman (1952) give considerable histological detail in their follow-up of 851 patients who had received irradiation for benign uterine haemorrhage. The histological findings at the time of irradiation were:

Endometrial hyperplasia	42 per cent
Proliferative phase	25 per cent
Secretory phase	17 per cent
Atrophic	7 per cent

Carcinoma followed endometrial hyperplasia in 3 cases; proliferative phase in 1 case; secretory phase in 1 case; atrophic endometrium in 3 cases.

Thus an equal number of patients developed carcinoma following the finding of hyperplasia or atrophy of the endometrium although there were 6 times as many patients in the group who originally had hyperplasia. This would seem to indicate that patients with an atrophic endometrium are more prone to develop an endometrial carcinoma.

Turnbull (1956) reported 4 cases of endometrial cancer, 2 of which had a normal endometrium at the time of prior curettage. The other two had an original diagnosis of cystic glandular hyperplasia.

The position is also obscured because most of the follow-up series are concerned with the effects of irradiation which was implicated by Corscaden, Fertig and Gusberg (1946) who found endometrial carcinoma in 9 cases out of 958 patients studied. Moreover, there were 5 further instances of the development of cancer outside the pelvis. This had previously been reported by Costolow (1941) who reported an incidence of development of malignancy of 0·3 per cent. Turnbull (1956) discovered that of 739 patients treated by irradiation for benign uterine haemorrhage, 4 patients developed endometrial cancer. In the present series neither patient had been irradiated at the time of the diagnosis of cystic hyperplasia but carcinoma developed none the less.

I feel that many authors have unintentionally given a misleading impression of the risks of carcinoma developing after a diagnosis of hyperplasia of the endometrium or following irradiation. Norris and Behney (1936) found that of 1,006 patients who had been irradiated 11 developed pelvic cancer. It is by no means certain that these represent cases of endometrial cancer. They based their conclusions that irradiation predisposed to endometrial carcinoma on the finding that the incidence of body malignancy to cervical cancer was 3 to 2 instead of the incidence they would normally have expected. Turnbull, however, found a body to cervix ratio of 2 to 3, a figure which he considered represented the relative incidence of malignancy of body and cervix in the Aberdeen district at that time.

In the discussion following the paper Pemberton reported the development of pelvic cancer in 4 cases out of 425 similar cases which he had followed up. In only one instance, however, was the cancer endometrial in origin, the cervix and the ovary being primarily involved in the other cases. Costolow (1941) reported the development of carcinoma of the uterus in 0·4 per cent of patients who had been treated by irradiation for benign uterine haemorrhage. There were 3 cases of endometrial cancer and 1 of cervix. There were 2 further instances of carcinoma of the ovary and again it was observed that in 8 patients carcinoma developed outside the pelvis, 6 times in breast and once each in stomach and kidney. The paper by Corscaden, Fertig and Gusberg (1946) is widely quoted on this subject. They followed up 958 patients who had had pelvic irradiation and

found that 35 patients subsequently developed malignant disease—an incidence of approximately 3·7 per cent. However, the uterus was involved in only 15 cases. There were 9 instances of carcinoma of the breast, 3 of rectum, 2 each of sigmoid, bladder and ovary, 1 of stomach and 1 of thyroid. But I think that, in any follow-up of from 10 to 20 years on almost a thousand patients aged 40–50 years, there is bound to be a certain incidence of malignant disease not necessarily related to the original pathological process. Moreover, of the uterine cancers 6 originated in the cervix. So the actual incidence of the development of endometrial carcinoma is just over 0·8 per cent. Of the 9 cases of carcinoma endometrial hyperplasia had been previously observed in 4 cases.

Barr and Charteris (1955) found 5 cases of malignancy developed in 850 patients treated by a radium menopause. Just over a quarter of the patients showed cystic glandular hyperplasia. There were 2 cases of endometrial carcinoma, 1 of carcinoma of cervix, 1 of rectum and a rodent ulcer.

Thornton, Nokes and Brown (1951) found 8 cases of 348 patients subjected to irradiation subsequently developed cancer of the pelvic viscera. There were 3 cases of sarcoma, 2 of which were myometrial in origin and the other endometrial. Surprisingly enough the former 2 cases followed endometrial hyperplasia but in the case of the endometrial sarcoma the endometrium had shown a simple secretory pattern at the original curettage. There was 1 case of cancer of the ovary which also followed an original diagnosis of endometrial hyperplasia.

Thus it is misleading if the author simply states that malignancy supervened in so many cases. Nor is it even satisfactory if the number of cases of malignancy of the pelvic viscera is given when the role of endometrial hyperplasia as a precursor is under consideration. Pelvic viscera includes rectum, bladder and ovary. I have shown too that "uterine malignancy" may be used to describe not merely endometrial carcinoma, but cancer of the cervix and sarcoma of the myometrium. When only endometrial cancer is being considered then the incidence of its development in follow-up studies is greatly diminished. Moreover, it does not develop solely in patients whose endometrium has previously shown hyperplasia. It frequently follows on normal endometrial patterns and is at least as likely to develop after a finding of atrophy of the endometrium.

Endometrial carcinoma is in the great majority of cases a condition affecting the post-menopausal woman and for the most part where endometrial hyperplasia has been noted as a precursor this finding has been made at the time of the menopause or even many years later.

Way (1954), Turnbull (1956) and Barr and Charteris (1955) have reported instances of this and have recommended more radical treatment of cystic hyperplasia in patients of this age group. On the other hand both cases in the present series occurred during the reproductive life of the women concerned and the development of carcinoma was detected before the onset of the menopause. A number of cases have been recorded in the literature of cases where carcinoma has followed hyperplasia in young women under the age of 40 years.

Hunter *et al.* (1954) described a case where the patient suffered from dysfunctional bleeding associated with endometrial hyperplasia at 30 years, and developed endometrial carcinoma 6 years later. Mazzola (1938) also reported on a patient where endometrial hyperplasia at the age of 18 years was followed by carcinoma when she was only 30 years old. One of Speert's (1949) cases showed hyperplasia at 21 years and carcinoma 16 years later. In this country Strachan (1936) reported a case of a patient with hyperplasia at 21 years and carcinoma 10 years later. Orrahood and Wyatt (1953) also described the development of carcinoma in a patient aged 20 years, 2 years after a curettage revealed cystic glandular hyperplasia. Purdie (1945) reported 2 cases of cancer of the corpus occurring in similar circumstances in sisters aged 34 and 32 years.

It seems, then, that endometrial carcinoma may follow an endometrial hyperplasia at any phase of a woman's life but the number of cases in which this develops is small. In the present series the incidence of the development of malignancy in cases of hyperplasia was less than 0·4 per cent. This very low incidence suggests that there must be some other factor involved

in the development of malignancy. Moreover, it has been shown that in some cases of endometrial cancer prior biopsy has often shown a normal proliferative or secretory phase or even atrophy of the endometrium.

Summary

(1) Patients in whom a diagnosis of cystic glandular hyperplasia had been made were followed up for periods of from 2 to 20 years.

(2) In 419 cases there was no further abnormal bleeding. One hundred and sixty-four patients had an artificial menopause induced by deep X-rays or radium.

(3) It was possible to examine the endometrium some years after the original diagnosis of hyperplasia in 78 instances. In younger patients reversion to a normal endometrial pattern frequently occurred. When the follow-up was over a considerable number of years, atrophy of the endometrium was more common.

(4) Malignancy was observed in 14 cases but there were only 2 examples of endometrial carcinoma, an incidence of 0·4 per cent approximately.

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THE EXCRETION OF FOLLICLE STIMULATING HORMONE BY PREGNANT WOMEN

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LITTLE is known about the existence of follicle stimulating hormone (FSH) in the urine of pregnant women. The concentration of human chorionic gonadotrophin (HCG) in their urine is so great that assays generally believed to measure FSH are invalidated by it. A new method has, therefore, been developed here (Butt, Crooke, Ingram and Round, 1957) which has now been used for the first time to study the pattern of excretion of FSH by women throughout normal pregnancy, and the results are reported in this paper.

MATERIAL AND METHODS

The subjects were 6 healthy women, all primiparae, whose ages ranged from 21 to 38 years. Pregnancy and labour were normal in all but one, the eldest, who had a Caesarean section for disproportion at full term. Urine was collected in 24, or occasionally in 48-hour lots, starting as soon as possible after the commencement of pregnancy. Three subjects provided samples at regular weekly intervals during the first trimester and thereafter at monthly intervals, but the other 3 were more irregular in their collections.

The method of extraction has been published in detail elsewhere (Butt *et al.*, 1957). It depends upon our observation that benzoic acid extracts about 80 per cent of the HCG from the urine of pregnant women but less than 10 per cent of the FSH from the urine of women after the menopause. The HCG is removed by extraction with benzoic acid and then the FSH is extracted by the kaolin adsorption procedure. In our preliminary work extracts were treated with tricalcium phosphate but subsequently this was not found to be desirable as some FSH is lost by adsorption (Butt and Round, 1958).

The method of assay which was developed in this laboratory has also been published in detail elsewhere (Brown, 1955). It depends upon the increase in weight of the ovary of the immature mouse treated simultaneously with an excess of luteinizing substance in the form of HCG so that the effect of any remaining luteinizing activity present in the test material is negligible. The HCG was obtained from the urine of one of the subjects by extraction with benzoic acid since not all commercial preparations are suitable. It was assayed against international standard HCG and a dose of 40 i.u. was given to each animal with the test solution. The new assay is suitable for statistical analysis and is believed to be fairly specific for FSH.

Each urinary extract was assayed against a standard, HMG20A, prepared for the Clinical Endocrinology Committee of the Medical Research Council by Organon Laboratories Limited, or against a similar laboratory kaolin standard which had been calibrated against HMG20A.

Usually insufficient FSH was obtained from a 24-hour specimen of urine for a satisfactory 2:2 point assay (2 dose levels each of standard and test material). Most of the assays were

therefore of 2:1 point design. It was observed that the lower dose of standard produced approximately a three-fold increase in ovarian weight. Provided the mean response of the test material was at least 50 per cent of the response of the lower dose of standard the result was calculated as a 2:1 assay. In other cases the result could not be calculated accurately and was reported as less than this equivalent of the standard. Such results are recorded as open circles in the figures. At least one specimen from each subject was assayed by a 2:2 point design in order to compare the slopes of the log dose-response lines with the standard. Satisfactory assays were obtained from all subjects but one, whose excretion of FSH was consistently too low.

Results

The complete results of about 50 assays are shown in Figure 1. They range from $<1 \cdot 8$ mg. to 13 mg. equivalents of HMG20A per 24 hours. The patterns of excretion in the 3 subjects from whom nearly complete collections were obtained are shown in Figure 2.

The log dose-response lines of some typical 2:2 point assays of extracts and standards are shown in Figure 3. These assays are satisfactory and are comparable with those reported previously by Butt *et al.* (1957). Only one out

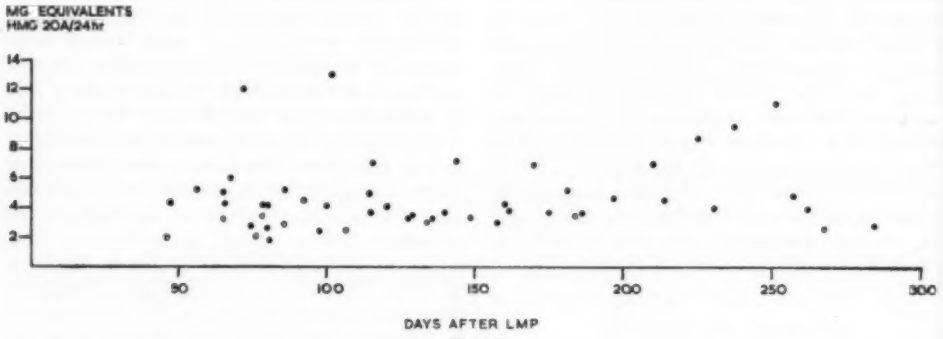

FIG. 1

Results in mg. equivalents of HMG2OA/24 hours. Open circles denote that the response was too small for an exact estimate to be calculated.

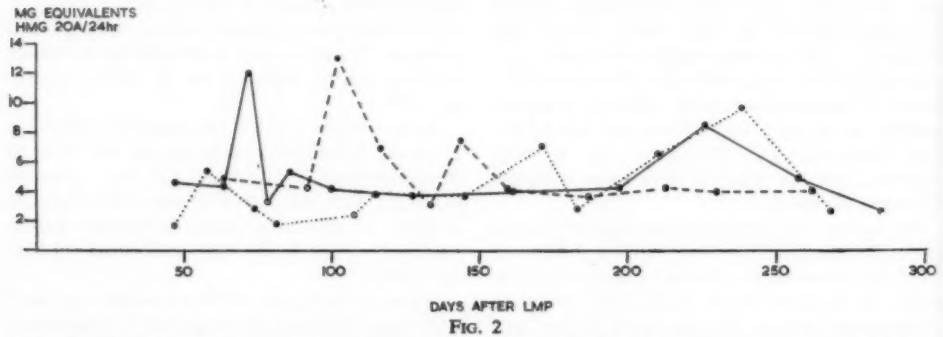

FIG. 2

Excretion of FSH by 3 women during pregnancy. Open circles denote that the response was too small for an exact estimate to be calculated.

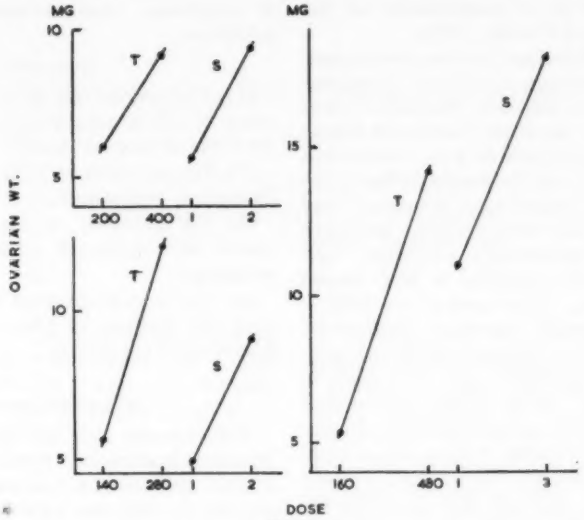

FIG. 3

Dose-response lines in three typical assays of FSH in pregnancy. T=test solution. S=standard (HMG20A). Dosages of T in ml. equivalents of urine of S in mg. There was no evidence of divergence from parallelism in the slopes of these lines.

of ten showed a significant divergence from parallelism in the log dose-response lines ($P=0{\cdot}01$–$0{\cdot}001$). This was an extract from a specimen collected 91 days after the last menstrual period (L.M.P.). Another assay from a specimen collected 125 days after L.M.P. showed considerable, but not significant divergence ($P=0{\cdot}05$–$0{\cdot}10$).

The amount of HCG excreted was assayed in some of these specimens. The benzoic acid extracts were used for these determinations as they contain nearly all the HCG (Butt *et al.*, 1957). The results from about 20 assays were between 3,000 and 45,000 i.u. per 24 hours, which are within the usually accepted normal range (Albert and Berkson, 1951; Loraine, 1950).

DISCUSSION

The biological activity of the substance which we have measured in the urine during pregnancy is similar to that found in the urine of women after the menopause. The evidence for its identity with FSH has been discussed previously (Butt *et al.*, 1957) and depends partly upon the parallelism of the log dose-response lines of the extracts and HMG20A. In nearly all the 2:2 point assays in the present series the degree of parallelism was excellent. There were only 2 doubtful cases in this series where the slopes were considerably different. Similar findings have sometimes been reported for extracts prepared from the urine of non-pregnant women (Brown, 1959) and the effect is thought to be due to some non-specific impurities.

The presence of FSH in the urine of pregnant women has been detected previously. Lyon, Simpson and Evans (1953) showed that extracts prepared by precipitation with alcohol caused follicular growth and the formation of corpora lutea in the ovaries of hypophysectomized rats, and Vignes, Robey and Simonnet (1954, 1955) obtained similar results with

extracts prepared by a modification of the method of Butt and Crooke (1953).

In the present investigations the daily output of FSH ranged between <1·8 and 13 mg. per day in terms of the standard HMG20A. Most figures were below the lower limit found during the normal menstrual cycle by Butt, Crooke and Cunningham (1958) and by Brown (1959) in this laboratory. Their ranges were between 5 and 87 mg. per day. They used a similar technique except for the preliminary extraction with benzoic acid which is unlikely to have caused a loss of more than 10 per cent of the FSH.

The low excretion persisted throughout pregnancy and there appeared to be no consistent pattern comparable with the peak in excretion of HCG which occurs in the first trimester nor with the fluctuations in the amount of FSH excreted during the normal menstrual cycle (Brown, 1959; Butt, Crooke and Cunningham, 1958). It may be compared with the pattern of excretion in most patients with secondary amenorrhoea of unknown aetiology in whom no fluctuation was found over the periods examined (Brown, 1959). In contrast with pregnant subjects, however, the amount excreted by these patients was in the same range as that found during the normal menstrual cycle. It would seem that their amenorrhoea was not due to a failure to secrete gonadotrophin by the pituitary gland but to a failure to vary production in a cyclical manner. The consistently low excretion of FSH during pregnancy is more like that found in a smaller group of patients with secondary amenorrhoea most of whom had severe wasting conditions like anorexia nervosa (Fletcher and Brown, 1957). Presumably they were all suffering from a failure of the pituitary to secrete gonadotrophin but the histological changes in the anterior lobe of the pituitary gland in pregnancy do not suggest pituitary failure and the low excretion in pregnancy must presumably be due to inhibition.

SUMMARY

(1) A technique has been developed for the assay of follicle stimulating hormone (FSH) in the urine of pregnant women.

(2) The excretion of FSH has been followed through 6 pregnancies.

(3) The excretion is consistently low and shows no significant variations throughout pregnancy.

(4) The amount excreted has been compared with the findings in other physiological and pathological conditions.

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PROLAPSE OF THE UMBILICAL CORD

BY

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PROLAPSE of the umbilical cord is an obstetrical complication which is associated with a high foetal mortality. Rhodes (1956) has estimated that at the present time in England and Wales this complication accounts for one in every 16 stillbirths, and Warnock (1958) has shown that, in the City of Belfast in the years 1946 to 1955, prolapsed cord was responsible for 2·9 per cent of the total stillbirths. The writer had the impression that at the Royal Maternity Hospital, Belfast, the foetal loss from prolapsed cord had in recent years been considerably reduced. In order to confirm or disprove this impression, an analysis of all cases of prolapse of the umbilical cord occurring in the hospital over a 15-year period was undertaken. In addition it was hoped to determine, if a reduction in foetal mortality had in fact occurred, whether any particular line of treatment had influenced this reduction, bearing in mind the fact that most recent authors, notably Cox (1951), Rhodes (1956), and Dilworth and Ward (1957) advocate the increasing use of Caesarean section in the treatment of cord prolapse.

During the years 1942 to 1956, there were 26,915 deliveries at the Royal Maternity Hospital, Belfast. Of these, 165 were complicated by prolapse of the umbilical cord, an incidence of 0·61 per cent or 1 in 160 deliveries. A comparison with the incidence reported from other centres is given in Table I.

AETIOLOGY

By definition, a cord cannot prolapse if the membranes are intact, and prolapse is unlikely if the presenting part adequately fills the pelvis. Therefore the factors predisposing to prolapse of the umbilical cord will be (1) factors preventing the close application of the presenting part to the lower pole of the uterus and brim of the pelvis, (2) factors causing rupture of the membranes when this state of affairs exists and (3) factors causing the presenting part to be

TABLE I

Incidence

	Deliveries	Prolapsed Cord	Incidence Per cent
Mengert and Longwell (1940), State University of Iowa, U.S.A. ..	9,546	63	0·66
Bourgeois (1941), Providence Lying-In Hospital, U.S.A.	36,773	155	0·42
Cope (1951), Leeds Maternity Hospitals	59,314	338	0·57
Rhodes (1956), St. Thomas's Hospital, London	15,355	83	0·54
Dilworth and Ward (1957), Shreveport, U.S.A.	19,893	66	0·33
Royal Maternity Hospital, Belfast (1958)	26,915	165	0·61

TABLE II

Predisposing Causes

Cause		Number of Cases	Primigravida	Multipara
Breech presentation:	Full	19	9	10
	Frank	10	5	5
	Footling	22	10	12
Shoulder presentation		31	3	28
Compound vertex		12	1	11
Brow presentation		1	—	1
Multiparity		20	—	20
Babies less than 5½ pounds		48	14	34
Abnormal pelvis		17	12	5
Multiple pregnancy		26	10	16
Placenta praevia		20	9	11
Foetal abnormality		6	3	3
Hydramnios		14	8	6
Artificial rupture of membranes		15	5	10
Dislodgement of head during forceps delivery		11	9	2
Excessive length of cord (over 75 cm.)		4	3	1

dislodged from the lower pole of the uterus and brim of the pelvis.

Predisposing causes in the present series are given in Table II. There is considerable overlap in this table as more than one cause may operate in any particular case. In 26 cases (16 per cent) no possible aetiological factor could be discovered.

Malpresentation. As with most other reported series, malpresentation of the foetus was a common aetiological factor. Breech, shoulder, compound vertex and brow presentation were found in 95 cases or 57·6 per cent of the total. Breech presentation was present in 51 cases, footling breech being the type most often associated with cord prolapse. Frank breech was found in only 10 cases of which 5 occurred in primigravidae. This would agree with clinical experience that frank breech, the commonest type of breech presentation in a primigravida, usually engages early in the pelvis and is seldom associated with cord prolapse.

Of 165 cases of prolapsed cord in the present series, 70 occurred in vertex presentations, 51 in breech presentations, 31 in shoulder presentations, 12 in compound vertex presentations and 1 in brow presentation. In the series of 100 cases reported by Kurzrock (1932), the presentation was vertex in 59, breech in 23 and transverse lie in 18. These figures give no idea of the relative frequency of prolapsed cord in the various presentations, as approximately 90 per cent of all presentations in the hospital practice are vertex presentations. Rhodes (1956) was able to show that, at St. Thomas's Hospital, London, the incidence of prolapsed cord was 1 in 412 with vertex, 1 in 18 with breech, 1 in 2 with shoulder and 1 in 10 with face presentation.

Multiparity. There were 20 cases in the present series in which multiparity was thought to be a contributing factor. In all of these the patient had delivered 5 or more babies previously. In only 8 cases was the presentation vertex. Usually it was a combination of premature rupture of the membranes and either an unengaged vertex or a malpresentation which led to the cord prolapse. Malpresentations are common in multiparae, being favoured by lax abdominal musculature and increasing foetal size with succeeding pregnancies. Even with vertex presentations the head often remains unengaged until after labour starts and some dilatation of the cervix has taken place. In such circumstances, if the membranes rupture prematurely, the natural conditions for cord prolapse are present. Bourgeois (1941) found that the incidence of prolapsed cord was 0·41 per cent in primigravidae and 0·43 per cent in

multiparae, but Slate and Randall (1956) found the complication almost twice as common in multiparae as in primigravidae and this also was the finding in the present series. It is generally recognized that the incidence of prolapse of the umbilical cord increases with increasing parity and Baird and Walker (1955) estimate that 90 per cent of all stillbirths in seventh and higher parities are due to malpresentations, prolapsed cord or precipitate labour.

Prematurity. Many writers pay little attention to the influence of prematurity on cord prolapse. There are several reasons why prolapse of the umbilical cord should be more likely with a premature baby. Malpresentations and malpositions are more common and breech presentation is directly related to prematurity as Vartan (1950) has shown. Even with a normal presentation a premature baby, by its very size, may be unable to fill the pelvis adequately and therefore space is left for cord prolapse to occur. Prematurity, as defined by weight, was present in 25 per cent of the series of 338 cases reported by Cope (1951). In the present series 48 out of 165 babies weighed less than 5½ pounds, an incidence of 29 per cent.

Abnormal Bony Pelvis. Malformation of the pelvis was considered by Schiller (1931) to be the most important predisposing factor in his investigation of 587 cases, but Mengert and Longwell (1940) found only 1 case of contracted pelvic inlet in 58 cases of prolapsed cord. Some authors, notably Gibberd (1955), have stressed the importance of a flat type of pelvis. In a flat pelvis the head tends to engage towards one side so that there is an unoccupied space in the opposite side of the pelvic inlet and through this space the cord may prolapse. In the present series, there were 17 women in whom a diagnosis of pelvic abnormality was made, an incidence of 10·3 per cent. In 11 cases the pelvis was described as flat and in 6 cases as generally contracted. The actual type of pelvis did not appear to be of importance, but rather the fact that the pelvic contraction was associated with malpresentation or non-engagement of the presenting part, so that when the membranes ruptured conditions were favourable for cord prolapse to occur.

Multiple Pregnancy. Prolapse of the umbilical cord was associated with multiple pregnancy in 26 cases (15·8 per cent) in the present series, twins being found in 22 cases and triplets in 4 cases. This incidence is much higher than that of 6·4 per cent given by Cope (1951) or 9 per cent in the series of Rhodes (1956) but approximates that of 18·3 per cent quoted by Gusberg (1946). In multiple pregnancy the smaller size of the foetus is an important factor, 16 of the 26 babies whose cords prolapsed having a birth weight of less than 5½ pounds, and also the fact that abnormal lies and presentations are common. The incidence of twin pregnancy is approximately 1·25 per cent of all pregnancies in this country and so the risk of prolapsed cord is greatly increased when twins are present. Most authors state that the danger is greatest for the second twin; this is not strictly true. The first twin is in danger because its cord is often implanted low in a very large placental area and some degree of placenta praevia may be present, and although the risk of the cord of a second twin prolapsing is certainly greater, the risk to the foetus is less as the cervix is fully dilated when the accident occurs.

Hydramnios. Cope (1951) found only 2 cases of hydramnios not associated with multiple pregnancy in his series and concluded that hydramnios does not seem to be of importance in the aetiology of prolapse of the cord. In the present series, hydramnios was associated with prolapsed cord in 14 cases (8·5 per cent), and in 6 of these multiple pregnancy was present. It would appear that in most of these cases the cord was carried downwards from above the level of the presenting part by the sudden gush of liquor when the membranes ruptured, and maladaptation of the presenting part to the pelvis was present. Gravity may also play a part in those cases where the membranes rupture with the patient in the erect position.

Placenta Praevia. In the present series, placenta praevia was associated with prolapse of the umbilical cord in 20 cases, an incidence of 12·1 per cent. In the series of Rhodes (1956) the corresponding figure was 5·4 per cent. Obviously prolapsed cord will not occur in Type IV placenta praevia unless the whole placenta is delivered in front of the presenting

part, and will be unlikely to occur in Type III placenta praevia unless the cervix is fully dilated. In Type I and Type II placenta praevia several factors tend to favour cord prolapse. The cord is often attached to the lower part of the placenta and is therefore brought nearer to the internal os. The presence of a placenta praevia, especially Type II posterior, will tend to interfere with engagement of the presenting part and thus favour cord prolapse, and also in placenta praevia the foetus is often premature. In 10 cases in the present series the foetus weighed less than 5½ pounds.

Dislodgement of the Head During Forceps Delivery. This occurred in 11 cases and followed manual rotation when the head was pushed out of the pelvis. There were no cases where prolapsed cord followed an attempt to correct an occipito-posterior position of the vertex before full dilatation of the cervix, and hydrostatic bags have not been used in the Royal Maternity Hospital, Belfast, for many years. Cope (1951), in the Leeds Maternity Hospital series, found 1 case of prolapsed cord which followed the insertion of a bag, and Slate and Randall (1956) had 4 out of 63 cases associated with the use of the Vorhees bag.

Artificial Rupture of the Membranes. Surgical induction of labour by artificial rupture of the membranes was associated with prolapse of the cord in 15 cases in the present series, an incidence of 9·1 per cent. In 14 cases immediate prolapse occurred, the forewaters having been ruptured. In the remaining case the hindwaters were ruptured using a Drew Smythe catheter and the cord prolapsed at a later stage. The details of the 14 cases in which immediate prolapse occurred are given in Table III. It will be seen that the presentation was vertex in only 6 cases and in 5 of these an additional factor predisposing to cord prolapse was present. In the series reported by Du Toit (1956) prolapse of the cord occurred only twice in 847 surgical inductions. In the Royal Maternity Hospital, Belfast, the most common form of surgical induction used is artificial rupture of the forewaters, and non-engagement of the vertex is not considered a contra-indication provided there is no cephalo-pelvic disproportion.

TABLE III
Artificial Rupture of the Membranes

Case No.	Presentation	Additional Predisposing Factor
1	Vertex	Flat pelvis
2	Vertex	Prematurity (3 pounds 12 ounces)
3	Vertex	Placenta praevia
4	Vertex	Placenta praevia
5	Vertex	Placenta praevia
6	Vertex	—
7	Breech—full	Placenta praevia
8	Breech—full	—
9	Breech—footling	Second of twins
10	Breech—footling	Hydramnios
11	Breech—footling	—
12	Shoulder	Hydramnios
13	Shoulder	—
14	Shoulder	—

Excessive Length of the Cord. Mengert and Longwell (1940) stressed a long umbilical cord as an important predisposing factor, and in the series reported by Slate and Randall (1956) there were 8 cases in which the cord measured 75 centimetres or more. Cope (1951) found the average length of the cord in his series to be 69·9 centimetres. Rhodes (1956) had a case in which the cord measured 135 centimetres. In the present series there were 4 cases in which the cord measured more than 75 centimetres. Excessive length of the cord would not seem to be an important predisposing factor. Prolapse of the cord outside the vulva may be more likely with a long cord but prolapse into the vagina will be just as common with a cord of normal length. Furthermore, a very long cord may become wrapped round the foetus and so be prevented from prolapsing.

DIAGNOSIS

Except in those cases where the prolapsed cord appears at the vulva, the diagnosis will be made only on pelvic examination. The diagnosis will be suggested if there is any alteration in the foetal heart tones, especially if this follows recent rupture of the membranes. Occasionally a prolapsed cord will be discovered accidentally when a pelvic examination is made for some other purpose, and it is important to remember that in the early stage of cord prolapse there may be no alteration in the foetal heart.

There is no doubt that the prognosis for the foetus worsens with increasing interval between diagnosis and the institution of treatment. In order that the diagnosis may be made as soon as possible, immediate pelvic examination should be performed (1) where there is any slowing or irregularity of the foetal heart, no matter what the presentation or the length of time since rupture of the membranes, (2) as soon as the membranes rupture in any case where a normal vertex is not engaged in the pelvis, or where any malpresentation exists, no matter whether the presenting part is engaged or not and (3) as soon as the membranes rupture in all cases of premature labour or twin pregnancy, even if the presentation is normal and the presenting part is engaged.

Factors Influencing the Foetal Prognosis

Of 165 babies, 60 were lost following prolapse of the umbilical cord, a gross foetal mortality of 36·4 per cent. A comparison with other series is given in Table IV and it will be seen that most authors report mortality rates varying between 30 per cent and 50 per cent. There were 17 cases in which the foetus was dead on admission to hospital. Therefore from 148 "treatable" cases, 43 babies were lost, an uncorrected mortality rate of 29 per cent.

An analysis of those cases where the foetus was lost was now undertaken in order to discover how various factors influenced the foetal prognosis.

Parity. Most authors state that the foetal mortality is twice as high in primigravidae as in multiparae and it might be thought that a lower mortality in multiparae would be expected because labour can be more easily terminated.

In the present series, of 49 primigravidae, 12 babies were lost (24·5 per cent) and of 99 multiparae, 31 babies were lost (31·3 per cent). This lower mortality in the primigravid patient can be explained, partly at least, by the more ready use of Caesarean section. The Caesarean section rate in cases of prolapsed cord was 32·6 per cent for primigravidae and 16·2 per cent for multiparae.

Presentation. Cope (1951) found that the mortality rate varied with the presentation, being 49·3 per cent with cephalic, 42·5 per cent with breech and 84·3 per cent with shoulder presentation. Slate and Randall (1956) also found that the mortality was higher in vertex than in breech presentations but less than in transverse lies. It would appear that vertex presentation produces the greatest degree of compression of the prolapsed cord, whereas the softer breech compresses the cord less and the irregularity of the breech allows more room for the prolapsed cord to be contained in the pelvis

TABLE IV
Mortality Rate

Source	Foetal Mortality
Mengert and Longwell (1940)	46·6
Bourgeois (1941)	49·7
Morgan (1948)	40·0
Brandeberry and Kistner (1951)	35·3
Slate and Randall (1956)	42·8
Rhodes (1956)	52·0
Royal Maternity Hospital, Belfast ..	36·4

TABLE V
Foetal Mortality and Presentation

	Total Number of Cases	Number of Deaths	Percentage Foetal Mortality	Number of "Treatable" Cases	Number of Deaths	Percentage Foetal Mortality in "Treatable" Group
Cephalic	83	31	37·3	75	23	30·7
Breech	51	15	29·4	48	11	22·9
Shoulder	31	14	45·1	25	9	36·0

without compression. The results of the present series support this view. As will be seen from Table V, 31 of the 60 gross foetal deaths occurred in cephalic presentations.

Prematurity. Prematurity has an adverse effect on foetal survival. When prolapse of the cord occurs in addition to prematurity, it would be expected that the life of the foetus would be doubly endangered.

In the present series, 48 out of 165 babies weighed less than 5½ pounds, an incidence of 29 per cent (Table VI). Of the 48 premature babies, 17 were lost. This gives a foetal mortality for the premature group of 35·5 per cent. Of the remaining 117 babies, 43 were lost, a mortality of 36·7 per cent. There is therefore no essential difference in mortality rates between babies weighing less than 5½ pounds and those weighing more than 5½ pounds. The reason for this may be that although the premature baby predisposes to cord prolapse, it inadequately fills the pelvis and therefore the cord tends to escape compression in the early stages. There is, however, another possibility. Excessive size of the foetus may also have an adverse effect on foetal mortality. In order to determine whether this is so, a breakdown of foetal mortality rates for babies of varying weights was made, and this is shown in Table VI. It would appear from this table that the baby of average weight, 6½ to 7½ pounds, has a much better chance of survival than the baby of lesser or greater weight, but it must be remembered that the treatment employed has an important bearing on the mortality figures.

TABLE VI
Foetal Mortality and Weight

Weight	Number of Cases	Number of Deaths	Percentage Mortality
Under 5½ pounds ..	48	17	35·5
5½ to 6½ pounds ..	21	7	33·3
6½ to 7½ pounds ..	36	9	25·0
7½ to 8½ pounds ..	34	18	52·9
Over 8½ pounds ..	26	9	34·6

Cervical Dilatation and Engagement of the Presenting Part. Most authors state that cervical dilatation is the most important single factor influencing the foetal prognosis. Kush (1953) found that, where the cervix was not completely dilated, the overall foetal mortality was 72 per cent. Fenton and D'Esopo (1951) found a direct relationship between foetal mortality and the station of the presenting part. Both these factors act by virtue of their determination of the treatment carried out. When the cervix is fully dilated and the presenting part is engaged, immediate vaginal delivery can be performed. A summary of the findings in the present series is given in Table VII. The 17 cases in which the foetal heart was not heard on admission to hospital have been excluded.

TABLE VII
Mortality, Cervical Dilatation and Engagement of Presenting Part

	Number of Cases	Deaths	Percentage Mortality	Caesarean Sections
Dilatation of Cervix:				
Less than 2 fingers (3 cm.)	26	6	23·1	20
2 fingers–¾	38	19	50·0	12
More than ¾	84	18	21·4	—
Presenting Part:				
Engaged	57	17	29·8	2
Not engaged	91	26	28·6	30

It can be seen that the use of Caesarean section has a profound effect on the prognosis in those cases where the cervix is not completely or almost completely dilated and the presenting part is not engaged. In the group where the cervix was less than 2-fingers dilated, only one baby survived which was not delivered by Caesarean section. This was a case of placenta praevia where the baby was considered too premature to justify abdominal delivery. The patient was subsequently delivered spontaneously and the baby survived. Obviously in this group, where there is a reasonable chance of obtaining a baby which will survive, Caesarean section is the only possible treatment.

In the group where the cervix was between 2-fingers and three-quarters dilated, the mortality rate was 50 per cent. One baby died following Caesarean section. The mortality rate in this group would have been much higher if Caesarean section had not been successfully employed in 11 cases. In this group lies the main hope of further reducing foetal mortality by the increasing use of abdominal delivery.

Treatment

In order to assess the value of treatment in foetal survival it is necessary to consider only those cases where the foetus was alive at the time of admission to hospital. There were 17 cases in which the foetal heart was not heard when the patient was admitted. Therefore, there were 148 "treatable" cases, and the influence of treatment on the foetal prognosis in these cases is given in Table VIII.

The treatment of prolapse of the umbilical cord depends in the first instance on whether the foetus is alive or dead. It is important to remember that absence of pulsation in the umbilical cord does not always mean that the foetus is dead as the heart may still be beating, and Cope (1951) delivered a baby by Caesarean section which survived after pulsation in the cord was stated to have ceased. If the baby is dead then no treatment for the prolapsed cord is indicated but of course any associated abnormality, for example shoulder presentation, must be treated. If the baby is alive then treatment depends on the dilatation of the cervix. If the cervix is fully dilated or almost so in a multiparous patient, then immediate delivery *per vaginam* by forceps or breech extraction should be carried out provided there is no contra-indication such as gross contraction of the pelvic outlet. Where immediate delivery from below is possible, no attempt should be made to replace the prolapsed cord as this only wastes time and, as will be stressed later, may cause spasm of the umbilical vessels. When the cervix is not fully dilated, the choice of treatment lies between Caesarean section and replacement of the cord.

Fenton and D'Esopo (1951) found that, if delivery could be carried out within half an

TABLE VIII

Foetal Prognosis and Treatment

Method of Treatment	Number of Cases	Stillbirth or Neonatal Death	Percentage Mortality
Delivery Immediate:			
Breech extraction in breech presentation	34	5	14·7
Internal version and breech extraction	15	5	33·3
Forceps delivery	32	9	28·1
Caesarean section	32	2	6·2
Delivery Delayed:			
Spontaneous delivery	18	11	61·1
Leg brought down, spontaneous delivery later	2	1	50·0
Leg brought down, breech extraction later	6	4	66·6
Bipolar version, spontaneous delivery later	8	5	62·5
Craniotomy	1	1	100·0

hour of prolapse of the cord, only 10 per cent of the babies were lost whereas, when the interval was longer, over 45 per cent were lost.

From Table VIII it will be seen that, in the present series, of 113 cases in which immediate delivery was carried out, 21 babies were lost, a mortality rate of 18·6 per cent, whereas of 35 cases, where delivery was delayed, 22 babies were lost, a mortality rate of 62·9 per cent.

Thirty-two Caesarean sections were performed with 1 stillbirth and 1 neonatal death, and the maternal mortality was nil. In the series of Cope (1951) 2 foetuses were lost from 42 Caesarean sections but there was one maternal death on the fourth day after delivery due to bilateral lower lobe collapse and bronchopneumonia, an open ether anaesthetic having been given.

Mengert and Longwell (1940) performed Caesarean section only once in their series of 58 cases and lost the foetus. They stated "Caesarean section was not generally used since it has not been considered justifiable to expose the mother to increased risk for a baby whose chances are so poor". They strongly advocated postural treatment in cases of cord prolapse where the dilatation of the cervix was small, but most writers now agree with the opinion expressed by Doerr (1947) that postural treatment is of little value except as a temporary measure while preparations are being made to deliver the patient by Caesarean section. Bourgeois (1941) considered that prolapsed cord in the absence of active labour, with both the mother and foetus in good condition, constituted a strong argument for Caesarean section and recent authors, notably Rhodes (1956) and Dilworth and Ward (1957), feel that the use of Caesarean section should be extended to nearly all cases where the cervix is not fully dilated. Caesarean section has been gaining in favour as a method of treatment for prolapsed cord at the Royal Maternity Hospital, Belfast, over the past 15 years. During the years 1942 to 1951, Caesarean section was performed in 14 per cent of "treatable" cases, that is, those in which the foetal heart was present on admission to hospital. The foetal mortality in these years from all cases of prolapsed cord was 33 per cent. In the years 1952 to 1956, Caesarean section was performed in 37·5 per cent of cases and the corresponding foetal mortality was 20·8 per cent. This is a step in the right direction, but the only way in which the foetal mortality can be reduced still further is by extending the use of Caesarean section to nearly all cases in which the cervix is not fully dilated when the umbilical cord prolapses. The author considers that the only contra-indications to Caesarean section should be (1) where immediate delivery by the vaginal route is possible without injury to the mother or foetus, (2) where the foetus is so premature that its chances of survival are poor, (3) where the foetal heart fails to recover after pressure on the cord is relieved and (4) where the foetus is known to be abnormal.

The alternative treatment by replacement of the prolapsed cord should be abandoned. In the present series, replacement of the cord was attempted on 32 occasions and was successful in only 19 cases of which 16 were multiparous patients. In these 19 cases, 10 foetal deaths occurred. Of the remaining 13 cases in which the cord could not be replaced, 5 babies died during the attempt and the remaining 8 were delivered without loss, 5 by Caesarean section where the cervix was less than three-quarters dilated, and 3 by breech extraction where the cervix was more than three-quarters dilated. Thus from 32 cases treated by cord replacement, 15 babies were lost (46·9 per cent). This compares most unfavourably with the results following Caesarean section, where from 32 operations 2 babies were lost (6·2 per cent). Rhodes (1956) comes down strongly against replacement of the cord. He points out that the circulation in a prolapsed cord almost certainly stops as a result of spasm of the umbilical vessels, and draws attention to experimental work by Barcroft (1946), who showed that with the sheep, as term approaches, the umbilical vessels tend to react to any kind of manipulation by contracting. Smith (1951) quotes work by Haselhorst (1929) who showed that the walls of the umbilical cord vessels are sensitive to temperature and to irritation from handling, and tend to react to these stimuli by contracting. Normally after birth, a sharply cut umbilical cord will bleed for six to ten pulsations, after which the flow gradually ceases provided the

end of the cord is in air. By placing the baby and the cut end of the cord in a water bath at body temperature, closure of the vessels is delayed and the cord will continue to bleed. The importance of these experiments is that, as Rhodes (1956) points out, when a cord prolapses, allowing it to cool or attempting to replace it may precipitate spasm of the umbilical vessels and cause death of the foetus. Replacement of the prolapsed cord into the uterus should therefore be avoided but gentle replacement into the vagina should be encouraged as thereby the cord can be kept warm and the risk of vascular spasm reduced while preparations are being made to deliver the baby by Caesarean section.

The main argument against the increasing use of Caesarean section is the fact that the operation is associated with a definite risk to the mother, especially as it may have to be performed urgently in a patient who has not been adequately prepared for a general anaesthetic. Marshall and Cox (1949) analyzed 7,762 Caesarean sections and found an overall maternal mortality of 0·99 per cent. For the lower segment operation, which accounted for 78 per cent of the total, the maternal mortality was 0·60 per cent. The lower segment operation was performed on 78 occasions for prolapse of the umbilical cord and in this group there were no maternal deaths. In a collected series from the American literature Marshall (1955) found 6 maternal deaths in 6,775 Caesarean sections, and of these 2 could not be attributed directly to the operation. This shows what can be accomplished and although most people would agree that it underestimates the risk, it is considered that the risk is a justifiable one in prolapsed cord if there is a reasonable chance of obtaining a living baby which will survive. Only by the increasing use of Caesarean section in the treatment of prolapse of the cord in those cases where the cervix is not fully dilated will the high foetal mortality associated with the condition be reduced.

Summary and Conclusions

(1) An analysis of 165 cases of prolapsed cord occurring at the Royal Maternity Hospital, Belfast, over a 15-year period is presented.

(2) The hospital incidence of prolapsed cord was 0·61 per cent or 1 in 160 deliveries.

(3) The major predisposing factors were abnormal lies and presentations especially breech presentations, multiple pregnancy and prematurity. Artificial rupture of the membranes and hydramnios were of minor aetiological importance and excessive length of the umbilical cord was not an important factor.

(4) The gross foetal mortality was 36·4 per cent. The foetal mortality for treatable cases, that is, those in which the foetal heart was present on admission to hospital, was 29 per cent. During the first ten years under review, the foetal mortality for treatable cases was 33 per cent. During the next five years, the mortality was reduced to 20·8 per cent and this reduction was associated with a marked increase in the use of Caesarean section as a method of treatment.

(5) The best prognosis for the foetus was given by immediate delivery. Where this was carried out, the foetal mortality was 18·6 per cent. Where delivery was delayed, the mortality was 62·9 per cent.

(6) Replacement of the prolapsed cord was associated with a foetal mortality of 46·9 per cent, and should be abandoned in favour of Caesarean section in most cases where the cervix is not fully dilated.

(7) Caesarean section was associated with a foetal mortality of 6·2 per cent and is the treatment of choice where immediate delivery *per vaginam* is impossible.

(8) There were no maternal deaths in the series.

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THE ONSET OF MENSTRUATION IN INDIAN WOMEN

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THE onset of menstruation or the menarche is one of the most dramatic events in the life of a woman. During puberty a series of complicated changes take place, controlled by the increase in the liberation of gonadotrophic hormones from the anterior lobe of the pituitary. Most of these changes cannot be measured but the appearance of the first menstrual flow can serve as a useful point to date the attainment of maturity. As it has been said (Mazer and Israel, 1951; Fairlie, 1957), the menarche provides an important landmark in the development of the individual and its timely appearance gives assurance that other, less recognizable features of puberty are developing normally.

Investigations have been carried out in several countries on the menarche and its possible interrelation with factors such as social status, diet, climatic conditions and race. The factors which have been cited by various authors as determining the age at menarche may be summed up under heredity, habitat and hormones.

Regarding the age at which menstruation begins, most authors (Mills, 1937; Purandare, 1945; Wilson and Sutherland, 1949, 1950; Ellis, 1950; Mazer and Israel, 1951; Bojlen, Rasch and Weis Bentzon, 1954; Patterson, 1957; Peters and Shrikhande, 1957) place the average age between 13 and 14 years with the range between 11 and 16 years.

It was originally believed that women living in the tropics mature earlier than women living in temperate or cold countries (Tilt, 1862). This has been shown to be incorrect by later workers. Mills (1937) stated that "quite the reverse has been found true, for in those regions of tropical moist heat, where body growth lags most, the menses are found to start distinctly later than in the invigorating temperate zones". According to him, sexual maturity in the tropics comes fully two years later than in temperate zones. In a comparative study by Ellis (1950) of a group of Nigerian girls and a group of nurses in Britain, the mean age at menarche was found to be slightly but significantly later in the Nigerian girls (14·22 years) than in the British girls (13·73 years). Ellis states that, besides climate, other environmental factors such as diet and the incidence of infection are vastly different in these two groups of women.

The importance of nutritional status is also stressed by Wilson and Sutherland (1949, 1950) in their studies of two series of English schoolgirls. These workers correlated the heights and weights of the girls with their age at menarche and found that the mean heights and weights were greater in those who had started to menstruate compared with those girls of the same age who had not.

Bojlen, Rasch and Weis Bentzon (1954) mention that in their series of 17,589 Danish girls, there was no significant influence of geographical distribution but that the menarche occurred about three months earlier on an average in the case of girls from a higher social milieu.

Experiments in animals (Ogle, 1934) have, however, shown that a hot moist atmosphere may retard sexual maturity when the diet is controlled.

Some workers (Mills, 1937; Mazer and Israel, 1951) are of the opinion that there is a distinct tendency towards the earlier onset of menarche and that in all countries the menses begin

earlier than was the case in the previous generation. Patterson (1957) in a study of 492 women in Edinburgh in 1957 found that the majority of the women in her series first menstruated between 13 and 14 years, in comparison with Kennedy's average of 15 years in Edinburgh girls of 1933 (Kennedy, 1933). This difference she ascribes to a possible improvement in diet, more exercise, and to the fact that the girls of today lead freer lives than those of previous generations. However, Wilson and Sutherland (1949) found no evidence of a decrease in the age at menarche of the girls interviewed as compared with the age at menarche of the mothers of these girls.

Material and Methods

The present study was undertaken by the Association of Medical Women in India with the object of determining the age at menarche in India today and finding whether it had any relation to the environment of the individual. For this purpose questionnaire forms were distributed to doctors as well as to girls' schools in various parts of the country. The questions included the present age, place of residence and community of those interviewed; their age at menarche and the age at menarche of their mothers; their rank in the family, state of literacy and economic status.

Information was obtained from 2,227 women in Trivandrum, Bangalore, Madras, Hyderabad, Bombay, Shillong, Lucknow, Gonda, Meerut and Kangra. Several difficulties arise in the evaluation of data from such a variety of sources. These difficulties are considered in relevant sections of this paper.

The Age at Menarche

This was obtained by the method of recollection. In the few cases where fractions of ages were stated, a period of 6 months and below was taken to the nearest lower age group while over 6 months it was taken to the nearest higher age group.

It might be argued that the information obtained by the recollective method is often inaccurate and that a girl is uncertain of her exact age at menarche even a short while after the event. This might apply in the case of a woman who does not even know her present age, but there is no doubt that the onset of menstruation is so impressive that a woman generally does remember the age at which it occurred. This is perhaps especially so in India where the appearance of the first menses determines whether or not the girl has reached a marriageable age.

Table I

Distribution of Age at Menarche

Age at Menarche	No. of Women	Percentage
9	2	0·1
10	12	0·5
11	87	3·9
12	441	19·8
13	739	33·2
14	538	24·2
15	234	10·5
16	133	6·0
17	26	1·2
18	8	0·4
19	4	0·2
20	3	0·1
Total	2,227	100·1

The average age at menarche in this group of women was 13·42 years with a standard deviation of 1·36 and a standard error of 0·03. This is very similar to the findings of Purandare (1945) who obtained an average age at menarche of 13·6 years in a group of 100 normal women, and of Peters and Shrikhande (1957) who state that more than half of their group menstruated between 13 and 14 years. The age at menarche in the present study is also about the same as that stated by European and American authors (Mills, 1937; Wilson and Sutherland, 1949, 1950; Ellis, 1950; Mazer and Israel, 1951; Bojlen, Rasch and Weis Bentzon, 1954; Patterson, 1957) so that there seems to be no basis for the old theory that girls in the tropics mature earlier than girls in colder countries. On the other hand, there was no indication that menstruation commences later in Indian women than in women from Europe or America. From Table I and Figure 1 it will be seen that the distribution of the age at menarche approximates

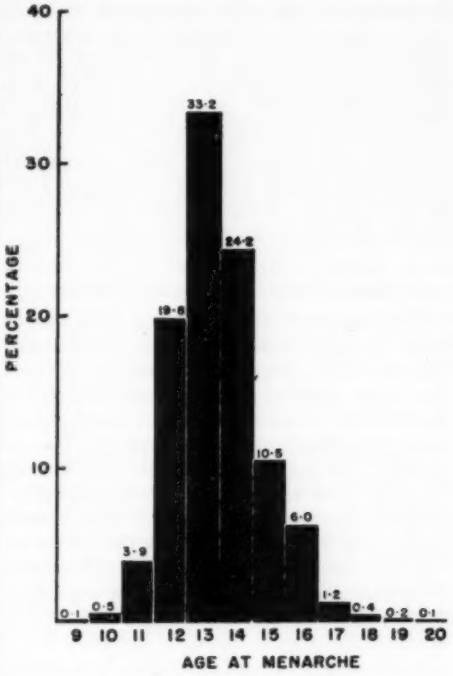

FIG. 1

Frequency distribution of age at menarche of 2,227 women.

to a normal Gaussian curve with a distinct peak near 13 years and flattening below 11 years and above 16 years.

THE COMPARISON OF THE AGE AT MENARCHE OF DAUGHTERS AND MOTHERS

In the present series it was possible to obtain the age of menarche of 1,053 mothers.

Table II and Figure 2 indicate the distribution of the mothers according to their age at menarche. The average age of menarche in the group of mothers was 13·59 years with a standard deviation of 1·48 and a standard error of 0·05, i.e., menarche had occurred about 2 months later in the mothers than it did in the daughters. This slight increase is for practical purposes insignificant, because fractions of ages

TABLE II

Distribution of Age at Menarche of Mothers

Age at Menarche	No. of Mothers	Percentage
10	3	0·3
11	39	3·7
12	183	17·4
13	334	31·7
14	282	26·8
15	107	10·2
16	58	5·5
17	21	2·0
18	20	1·9
19	4	0·4
20	1	0·1
21	1	0·1
Total	1,053	100·1

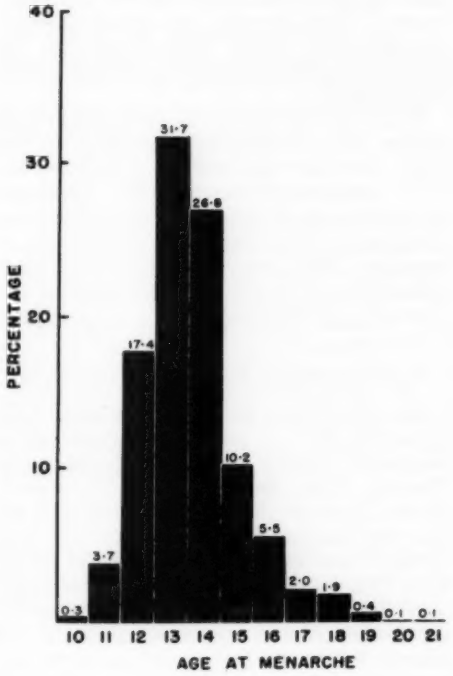

FIG. 2

Frequency distribution of age at menarche of 1,053 mothers.

have, in most cases, not been stated by the women interviewed.

A more accurate idea of the comparison of the mothers' age at menarche and that of the daughters was gathered by grouping each mother-daughter couple according to the difference in their stated ages at menarche. In 29·8 per cent there was no difference in the age at which menstruation commenced. In 17·8 per cent the mothers had menstruated one year later than the age at which their daughters had menstruated and in 23·6 per cent they had menstruated one year earlier than the age at which their daughters had done so. It is interesting to speculate on the reason for this difference between our findings and those of other workers. It is a well-known fact that the Indian girls of today, particularly those from certain conservative communities, lead more vigorous lives than their mothers did. With regard to diet, however, we cannot say there has been any radical improvement. On the contrary, the diet of the mothers may have been slightly better.

By correlating the ages at menarche of each mother and corresponding daughter, it was found that the coefficient of correlation was 0·276 which indicates that the correlation between the age at menarche of the mothers and daughters was very weak. The mother's age at menarche does not, therefore, have much influence on the age at which her daughter will commence menstruating.

Age at Interview and Age at Menarche

The advantage of the recollective method lies in the fact that it is possible simultaneously to interrogate women born in different years. However, it may be that the older the woman, the less accurately is she able to remember her age when menstruation commenced. The ages of the women interviewed in this series ranged from 12 to 60, but the majority (93·6 per cent) were below 30 years. A comparison of the distribution of the age at menarche in the various 5-year age groups did not show any significant difference in the average in the age groups above 16 years. In the 10 to 15 year group, the average was lower (12·71 years) than those of the other age groups or of the whole series. This lowering of the average is expected since this age group does not include girls of 16 to 20 years in which latter group normal menstruation can still occur. If the 10 to 15 year age group is combined with the 16 to 20 year age group, the average age at first menstruation in this combined group was found to be 13·32, i.e., it approximates to the average ages in the higher age groups.

Economic Level and Age at Menarche

The women were divided into three groups: those in economically straitened circumstances (income below Rs.150/- per month), those in the lower middle class (income Rs.150/- to Rs.500/- per month) and those in economically easier circumstances (income over Rs.500/- per month). The average age at the menarche was found to be lowered in the girls belonging to a higher economic group, the difference between the average age at menarche in the lowest and highest income groups being about 6 months. This needs further investigation in a group of women in whom the exact age at first menstruation to the nearest month is known.

It may be mentioned here that it is possible that the interviewers varied in their interpretation of the economic status. Some may have understood it to mean the present economic state of the interviewed women, while others might have considered it to be their economic level at the time of attaining puberty.

Literacy and Age at Menarche

There was no difference in the age at menarche among the literate and illiterate women in this series.

Rank in Family and Age at Menarche

The age at menarche of the group of first- and second-born children did not differ from that of the groups of third and fourth, fifth to seventh and eighth to thirteenth children. Unless, however, one can compare the ages at menarche of siblings, in whom the environmental factors are more or less similar, this finding is not of much significance.

Climatic Conditions and Age at Menarche

The women in this series were from various parts of India. The climatic conditions in these places vary widely, for instance Bombay and Trivandrum have a hot, wet climate, while Lucknow is comparatively dry with extremes of heat and cold and Shillong and Kangra have a cold climate with heavy rainfall. The average age of the menarche was found to be higher (15·02 years) in Trivandrum than it was in other places. Whether this is owing to the fact that the climate of Trivandrum is hot and moist for the greater part of the year, or whether it is because of the low economic level of the women interviewed, requires more detailed investigations.

Community and Age at Menarche

The information available about the community of the women interviewed was very variable. Some investigators made a special mention of sub-groups whereas others made a more general classification. It was decided to classify the women into five broad communal groups, viz.:

(1) Hindus (a small number of Sikhs, Jains and neo-Buddhists were also included in this group)
(2) Muslims
(3) Christians
(4) Parsis
(5) Jews

and to these a sixth group of Assam Tribals was added. This last group included those Tribals whose religion was not mentioned as well as those whose religion was specified.

The heterogeneous nature of the Hindu, Muslim and Christian groups, which include persons from various parts of the country, from various economic levels and with varying dietary habits, makes them unfit for statistical comparison. The Jewish group was too small to be of any significance but it is interesting to note that the average age at menarche was low (12·5 years).

Perhaps the only groups which are of much interest are the fairly homogeneous Parsi group all of whom were from Bombay, and the group of Assam Tribals. In neither of these was there found any marked deviation of the average age at menarche from the average age of the whole series.

It was felt that many of the women attending the general hospitals might have abnormal menstrual functions and their inclusion in the whole group might shift the age of menarche away from the normal range. It was also thought that the inclusion of the group of school children who have already begun to menstruate might lower the age at menarche. The series was therefore grouped as follows:

(1) School children.
(2) Normal women students (undergraduates and postgraduates).
(3) Women attending postnatal clinics.
(4) Women attending general hospitals.
(5) Women attending private clinics.

A comparison of these five groups showed that between 50 to 60 per cent of the women in each group had their first menstruation between 13 and 14 years.

Concluding Remarks

It is obvious that such a study can only give a very general idea of the onset of the menarche in Indian women. The number of women interviewed is far too small to enable the application of the findings to the whole country. More accurate information would be obtained by a detailed investigation of certain endogamous groups of Indian women rather than by including in the study a wide variety of women in whom the only common feature is their Indian nationality.

Summary

(1) Two thousand two hundred and twenty-seven women from various parts of India were interviewed regarding their age at menarche.

(2) The average age at menarche in this group of women was 13·42 with a standard deviation of 1·36. This is similar to the age at menarche quoted by other workers in India and by western authors.

(3) The distribution of the age at menarche was found to approximate to the normal Gaussian curve.

(4) The average age at menarche of the mothers of 1,053 women in this series was found to be 13·59 years with a standard deviation of 1·48.

(5) There was no significant difference in the age at menarche in a comparison of the mothers' and daughters' ages at menarche.

(6) The mother's age at menarche did not appear to have much influence on the age at which her daughter commenced to menstruate.

(7) There was no significant difference in the distribution of the age at menarche in the various age groups above 16 years. In the age group 10 to 15 years, the average age at menarche was lower. If, however, the age groups 10 to 15 and 16 to 20 were combined, the average age at menarche in the age group 10 to 20 was similar to that of the whole series.

(8) The age at menarche was lower in girls from the higher income groups than in girls from less well-to-do homes.

(9) There was no correlation between the state of literacy of the individual and her age at menarche.

(10) The rank of a girl in her family did not appear to influence her age at first menstruation.

(11) Trivandrum showed a slightly but significantly higher age at menarche compared with the other places.

(12) The two homogeneous communal groups, viz., the Parsis and Assam Tribals, did not show any marked deviation of the age at menarche from the age at menarche of the whole series.

(13) No difference in the age at menarche was found in the various classes—schoolgirls, women students, etc.—of the women interviewed.

I am grateful to the Association of Medical Women in India and to the secretaries of its various divisions for providing the material on which this paper is based. I am also grateful to all those whose untiring help and valuable suggestions made the preparation of this paper possible.

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THE CERVIX IN HYSTEROSALPINGOGRAPHY

BY

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It is now recognized that the cervix is not merely a rigid canal, but a dynamic structure with a functioning sphincter at the level of the internal os (Westman, 1942; Palmer and Liesse, 1946; Schild, Fitzpatrick and Nixon, 1951; Hughesdon, 1952; Borell and Fernström, 1953; Youssef, 1957). The chief drawback of the traditional type of cannula used in hysterosalpingography is that the tip of the instrument enters the cervical canal for an appreciable distance and obscures its outline. Contrast medium is injected direct into the uterine cavity, and the cervix is by-passed. Furthermore, techniques which allow the cannula's tip to pass through the isthmus, such as those used by Rubovits, Cooperman and Lash (1953) and Green-Armytage and Browne (1957), may give a misleading impression of this region, while the Leech-Wilkinson type of cannula is particularly likely to distort the cervical canal.

For these reasons the need arose for a cannula which would neither pass through the internal os nor distort the cervical canal. Only thus could the true appearance of the canal be demonstrated, and a reliable diagnosis of incompetence of the internal cervical os be made.

Asplund (1952) and Johanson (1956) have described instruments which satisfy these requirements, but are mechanically unwieldy and complicated. The short tipped cannula used by Fullenlove (1953) in my hands too frequently fails to give an adequate seal at the cervix.

Hunter and Henry (1955) described a more practical instrument which has now, with minor modifications, been made for me by Messrs. John Bell and Croyden of London.

The instrument consists, basically, of a straight cannula, 26 cm. long, having at one end a Luer fitting mount, and at the other a screw thread superimposed, 25 mm. from the tip, and extending for a length of 35 mm. On to the thread is screwed a silver cup, 20 mm. in diameter and 10 mm. deep, having at one point an obliquely cut slot. A balloon type of catheter, of suitable gauge and of 30 ml. capacity, is adapted to the cannula by the removal of that part distal to the balloon, and by the cutting of a lateral notch immediately under the balloon. The distal end of the cannula has been strengthened in order to accommodate a post to which tenaculum forceps can be attached.

The instrument is assembled by screwing the cup on to the cannula, followed by the passing of the balloon over the tip of the cannula. The balloon is now inflated and seats down into the cup. Enough of the cannula (approximately ½ cm.) projects to secure a hold in the cervical canal, and the inflated balloon forms an effective seal between the concavity of the cup and the convexity of the cervix (Fig. 1).

Two single-toothed tenacula are used to supply countertraction and a better seal is obtained if they are applied laterally rather than antero-posteriorly. The balloon is inflated by means of a syringe to a size which must vary with that of the cervix under examination. Usually 5 to 10 c.cm. of air suffice.

Satisfactory X-rays of the cervix, uterus and tubes are obtainable with this instrument. In cases with tubal obstruction it is occasionally difficult to obtain a perfect seal; therefore, for the investigation of cases of subfertility I continue to employ the traditional rubber olive

tipped cannula, but the instrument described is ideal for the investigation of cases of repeated abortion.

There are further advantages associated with the use of the short tip cannula: as pointed out by Hunter and Henry (1955), it avoids the pain associated with the passage of the traditional type of cannula through the internal os; reflex tubal spasm due to endometrial trauma is avoided. Furthermore, in cases of bicornuate uterus, it avoids the confusion caused by passage of the long cannula into one horn only.

In the X-rays here submitted, the technique of examination was that described by Reiss and Grossmann (1958) and Urografin 76 per cent was the contrast medium employed.

Various appearances of the normal cervical canal are shown in Figures 2 and 3. Figures 4 and 5 show the funnel-shaped cervix (Jeffcoate and Wilson, 1956) and the grossly incompetent cervix frequently associated with habitual abortion.

Finally, Figure 6 shows how, in a uterus bicornis bicorpus unicollis, passage of the traditional type of cannula into one horn may fail to outline the second horn, unless repeated pictures are taken and there is adequate reflux from one side to the other. Figure 7 shows the immediate filling obtainable with the short tip cannula.

Acknowledgments

I am greatly indebted to Dr. Maria Grossmann and the staff of the X-ray Diagnostic Department for taking the X-rays; and to Mr. D. S. Petch of Messrs. John Bell and Croyden, for his help in manufacturing and modifying the cannula.

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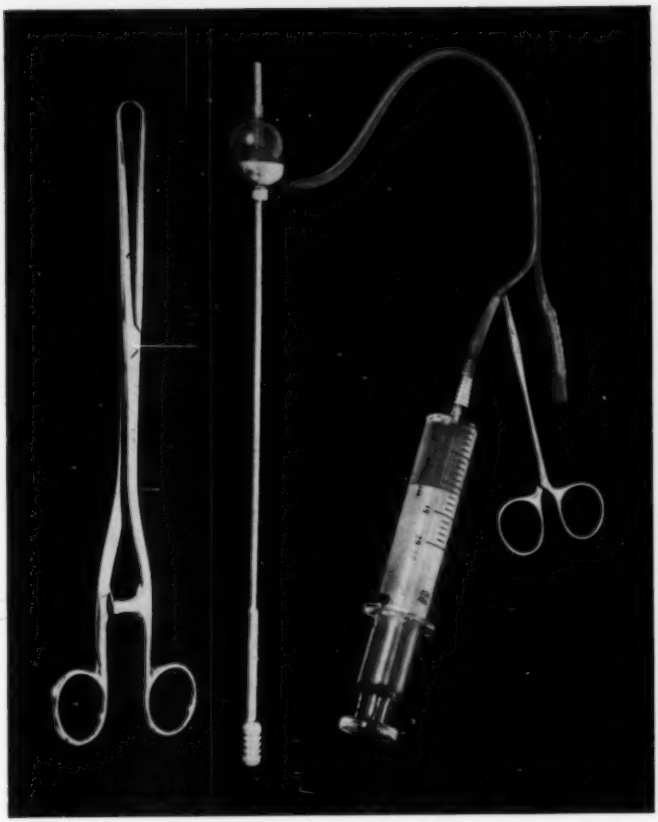

FIG. 1
Instrument—assembled for use.

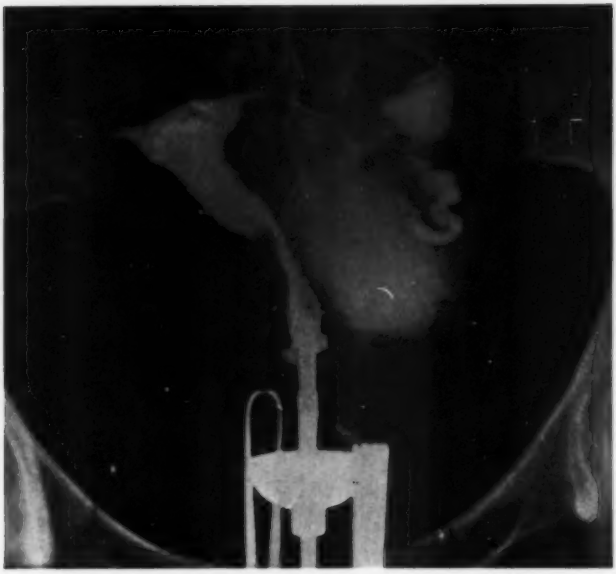

FIG. 2
Normal cervical canal.

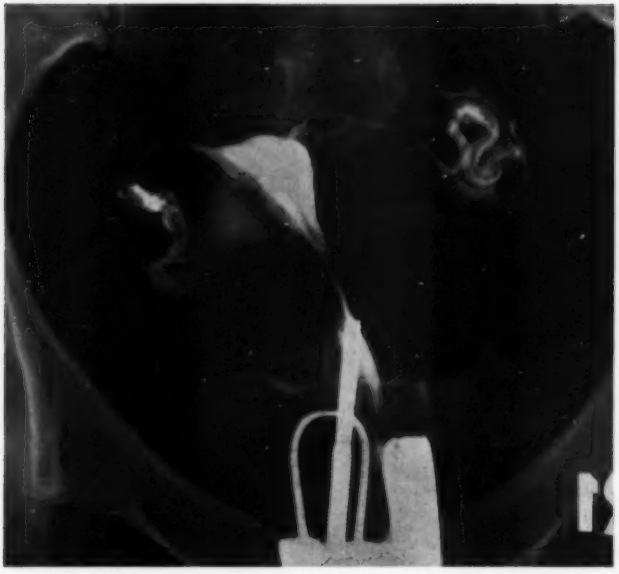

FIG. 3
Normal cervical canal.

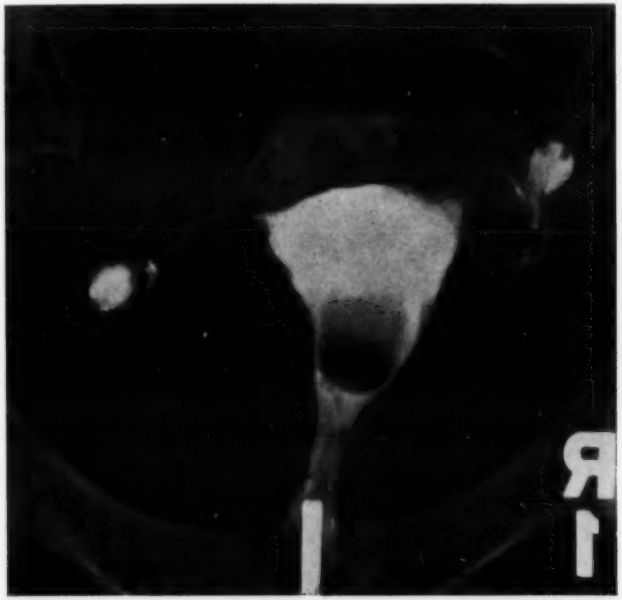

FIG. 4

Funnel-shaped isthmus and cervix from a patient with habitual abortions.

FIG. 5

Wide cervix in a patient with 3 late abortions following precipitate labour in the first pregnancy.

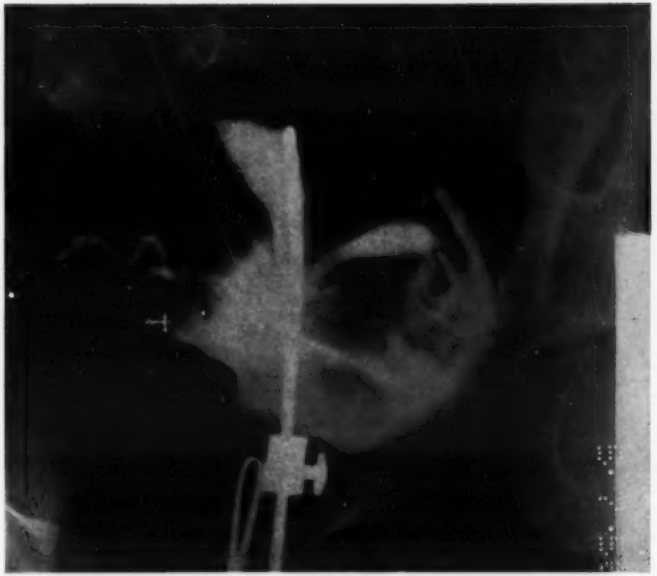

FIG. 6

Uterus bicornis bicorpus unicollis demonstrated only with difficulty at the third exposure, due to passage of cannula into one horn.

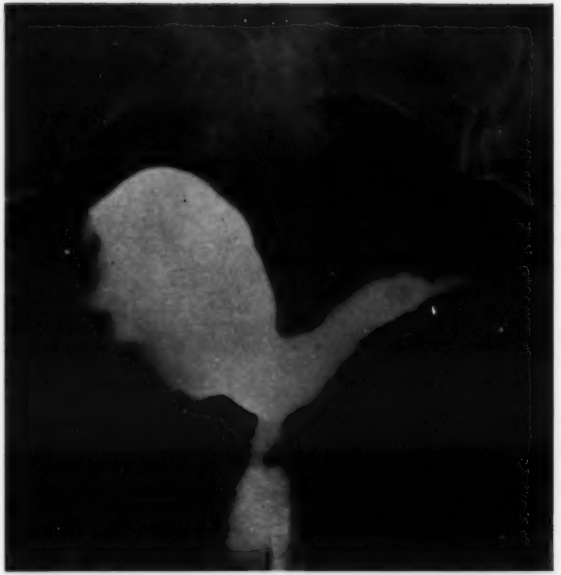

FIG. 7

Uterus bicornis bicorpus unicollis, in a patient with multiple submucous fibroids in one horn, and intramural fibroids, easily outlined by short tip cannula.

SYMPOSIUM ON PRENATAL CARE

DURING the week preceding the World Congress on Sterility and Fertility a Symposium on prenatal care will take place in Groningen and Rotterdam from 1st to 6th June. (The World Congress will take place from 7th to 13th June, 1959.)

PROGRAMME

Monday, 1st June

"Oestrogenic hormones in pregnancy (determination, excretion, significance)." Lectures by Marrian (Edinburgh), Finkelstein (Tel Aviv), ten Berge (Groningen), Weeke (Groningen).

"Foetal hypoxia." Lecture by Jonxis (Groningen).

"The neurological picture in the newborn, after pre- and paranatal hypoxia." Lecture by Prechtl (Groningen).

"Foetal haemoglobin." Lecture by Visscher (Groningen).

Tuesday, 2nd June

Twelve lectures on "Diabetes and pregnancy". Lecturers (among others): Gaarenstroom (Groningen), Dietel (Hamburg), Mestwerdt (Hamburg), Thomson (Hamburg), v. Bouwdijk Bastiaanse (Amsterdam), Vague (Marseille), ten Berge (Groningen), Weeke (Groningen), Doornbos (Groningen).

Organization of prenatal care in Israel (Asherman) and in the Netherlands (Staal and Janssens).

Wednesday, 3rd June

"The thyroid gland and pregnancy." Lectures by Querido (Leiden), Woldring, Weeke and Bol (Groningen), Holmer and Birnie (Leiden).

In the afternoon lectures on "Sterility" by Bravo (Mexico), Williams (Springfield), Marburger (Innsbrück), Asherman (Tel Aviv), and Palmer (Paris).

Thursday, 4th June

Excursion.

Friday, 5th June

"Adrenals and pregnancy." Lectures by Bravo (Mexico), Overbeek (Oss), Schmidt and Horman (Rotterdam).

"Cytology and pregnancy." Lectures by Murray (Buenos Aires), Campos da Paz (Rio de Janeiro), and Bulterijs and de Neef (Rotterdam).

Saturday morning, 6th June

"Spermatogenesis." Lectures by Williams (Springfield), Hellinga (Amsterdam), Blijham and Schellen (Groningen), Swaab (Amsterdam).

Discussion by Bravo, Vague, Marburger, Asherman, Palmer, and those attending the symposium.

Symposium fees	50 Dutch guilders.
Hospital assistants	25 Dutch guilders.
Ladies programme	50 Dutch guilders.

Programme and information: Prof. Dr. B. S. ten Berge and Dr. A. Weeke, University Hospital, Groningen, the Netherlands; Dr. A. L. C. Schmidt, Hospital Coolsingel, Rotterdam, the Netherlands.

REPORTS OF SOCIETIES

GLASGOW OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

October 1958

A Meeting of the Glasgow Obstetrical and Gynaecological Society was held on Wednesday, 15th October, in the rooms of the Royal Faculty of Physicians and Surgeons. The President, Dr. W. C. Armstrong, was in the Chair, and Dr. Mary G. Coyle addressed the Society on the

Urinary Pregnanediol Assay and Its Clinical Application

She discussed briefly methods of extracting and purifying pregnanediol and drew a comparison between the older precipitation techniques and the more recent chromatographic method of Klopper, Mitchie and Brown. The results obtained in 10 cases of normal late pregnancy using this method were illustrated diagrammatically to show that close correlation was found when two people independently performed duplicate assays on the same specimens of urine.

The lecturer then showed a series of slides to illustrate the range of excretion in cases of normal and of abnormal pregnancy. The series was divided into two parts: firstly, cases under observation in Sheffield during the years 1954–1957; secondly, cases studied in Dundee from November, 1957 to July, 1958. In toxaemia, essential hypertension, accidental haemorrhage, it was shown that in both series sustained low levels of pregnanediol excretion were associated with poor foetal growth and development and sometimes with foetal death. In 4 cases of severe toxaemia under observation in Dundee, the excretion was maintained at a level under 10 mg. between the 28th and 35th weeks of pregnancy and foetal deaths occurred.

Caesarean sections were performed on 3 elderly patients who had severe toxaemia and a low level of excretion; the babies delivered between the 33rd and 34th weeks of gestation survived. Labour was induced by pitocin drip and surgical rupture of membranes in 2 young women who developed a severe fulminating type of toxaemia at the 33rd and 34th weeks of pregnancy because foetal growth, judged clinically, was poor and pregnanediol excretion was maintained at a subnormal level: the babies, although weighing only 3 pounds and 3 pounds 4 ounces respectively, survived.

The level of excretion in other cases where the obstetric history was poor was also presented, and it was shown that this assay was often of value in the management of that type of patient.

In conclusion Dr. Coyle suggested that the pregnanediol assay might be used as an index of placental function provided:

(1) Only accurately collected 24-hour specimens of urine are assayed.

(2) A reliable method is used for extracting and purifying the urinary pregnanediol.

(3) Interpretation of the results is related to the patient's clinical condition: subnormal levels of excretion are not an indication for termination of pregnancy unless the patient's condition is deteriorating or foetal growth, judged clinically, is poor.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

October 1958

A Joint Meeting of the North of England Obstetrical and Gynaecological Society and the Section of Anaesthetics of the Manchester Medical Society was held in Manchester on 17th October, 1958. Dr. E. A. Gerrard and Dr. M. O'Grady presided.

The subject of the meeting was

Anaesthesia in Obstetrics

Dr. Trevor Johnson opened the proceedings.

Successful obstetric anaesthesia was first demonstrated by Simpson in 1847, and though techniques have changed the purpose to relieve suffering and facilitate operative delivery has not altered. Simpson believed general anaesthesia would reduce the incidence of stillbirth and maternal death, and this has proved true where complicated delivery is concerned, though regional anaesthesia may afford even better results.

The transition from uterine to extra-uterine existence is still one of the most hazardous experiences of a lifetime for both mother and child. Foetal existence depends on the placenta, and, although the placenta transmits excess quantities of electrolytes, its ability to transmit oxygen is poor. The reserve of placental capacity is small and easily impaired by such conditions as postmaturity, maternal hypertension or a prolonged first stage of labour. It is vital to the foetus to avoid maternal anoxia, and to bear in mind that she is predisposed to this from her increased metabolism and reduced vital capacity and the splinting of the diaphragm by the uterus.

Asphyxia was among the commonest causes of stillbirth and maternal death. It accounted for 32 of 49

maternal anaesthetic deaths in Great Britain between 1952 and 1954, and was largely due to blocking in the airway by regurgitated gastric contents. Vomiting in labour is aggravated by the delay in gastric emptying and the use of morphia. Incomplete preparation of the patient and the need for speedy delivery aggravate matters. Moreover the plethora of drugs demands close co-operation between obstetrician and anaesthetist to avoid antagonistic effects.

Careful mental and physical preparation of the patient in the antenatal clinic is an important contribution to successful anaesthesia. Improvement in anaesthetic technique and a competent anaesthetic service have assisted in the decline of maternal and perinatal death. In a busy unit between 15 and 20 per cent of patients require some form of anaesthesia at delivery, and because of the irregular demands it is inevitable that much of the responsibility rests with the resident anaesthetist or the obstetrician, and one-third of all confinements still take place at home.

The recent survey of maternal death in England and Wales suggests that greater opportunity of saving life lies in domiciliary practice, and so we have a responsibility to acquaint our house surgeons with suitable techniques. They should become adept at pudendal analgesia. It is applicable to the type of obstetric operation, safe in domiciliary practice, and more difficult procedures are best done in hospital or left to the Flying Squad.

Some questions still have not a ready answer. What is the nature of pain in labour and its sensory pathway? Could not a safer anaesthetic or analgesic be devised which could be confined to the maternal circulation? Is there scope for extending the anaesthetic service to domiciliary practice? Has a labour ward bed yet been devised to suit all needs and allow speedy tilting, and lastly does the labour ward diet receive sufficient attention?

Dr. A. Mackenzie read the second opening paper.

Obstetric anaesthetics come into a class of their own, first because it is the only time we anaesthetize two patients, and send one partially anaesthetized patient off to establish existence in a strange environment, and second, with few exceptions, all are anaesthetic emergencies. Sufficient muscular relaxation is required to allow easy operation, but not at the expense of uterine tone or neonatal asphyxia. The biggest risk is the aspiration of stomach contents, and where death is deemed to be due to the anaesthetic, or the anaesthetic and surgery combined, this appears to be the cause in no less than 24 per cent of cases. Of the patients who aspirate stomach contents, only a small proportion die, the degree of morbidity is difficult to assess, and the maternal anoxia is the most potent method of depressing the foetus.

Women in labour are prone to delayed gastric emptying, and though they cannot be starved, it would be reasonable to withhold solid food, so that the stomach can be emptied by a small bore tube.

Sedatives before the anaesthetic are best avoided, and usually atropine only is given. The actual technique will reflect the individual technique in other surgical cases with due allowance for the special problems. For a set procedure, intravenous thiopentone followed by a relaxant, tracheal intubation and maintenance on nitrous oxide and oxygen is suitable. In emergency cases on inhalational induction, intubation without a relaxant followed by nitrous oxide and oxygen can be employed. The time factor in this second procedure is not significant.

Barbiturates are potent respiratory depressants even in small dosage. Vomiting with barbiturates is rare, but respiratory depression and laryngeal spasm is not a happy combination. With a relaxant passive regurgitation and flooding of the pharynx and trachea with stomach contents may occur despite an oesophageal tube. There is as yet no safer form of induction in emergency cases than a brisk inhalation method using ether or cyclopropane. Vomiting can only occur with breath holding, and if the respiratory drive is such that the patient cannot hold her breath, then she cannot vomit. When the jaw relaxes, intubation is performed, and inhalation is continued with nitrous oxide and oxygen.

Serial samples of blood from patients undergoing different types of anaesthesia were estimated for blood ether levels, and in a few cases of Caesarean section samples of cord blood were obtained at the moment of clamping. The results showed that it was reasonable to continue using an inhalational induction followed by endotracheal intubation in the majority of cases.

Mr. O. V. Jones: In obstetrics, anaesthesia must not only facilitate the manœuvre but be safe for mother and baby. In emergency cases with inadequate preparation and the trained services of an anaesthetist often wanting, we need a simple and safe routine. Experience in a rural obstetric unit has shown the simple methods are the safest.

In 25,000 deliveries over a 20-years period, there were 1,750 Caesarean sections, 2,745 forceps deliveries and 870 breech deliveries, with 2 maternal "anaesthetic deaths". During the first 10 years open ether was the method used, but latterly with a competent anaesthetist available other methods have been employed.

In the last 5 years increasing numbers of deliveries were conducted under pudendal block, the incidence now reaching 70 per cent for forceps deliveries. Because of the many emergencies that occur, open ether would seem safest in the hands of inexperienced staff.

For breech delivery a technique has been worked out, and since 1954 in 138 cases, local analgesia, in some cases with the addition of thiopentone, was employed in 60·9 per cent of cases, and in 18·1 per cent of cases open ether or thiopentone, nitrous oxide, oxygen and ether. The remainder required no analgesia. Two infants only were lost.

In the first 5 years of the review many different anaesthetic methods were used for Caesarean section. Later gas, oxygen and ether or cyclopropane were employed with reduction of foetal loss. For the last

10 years a trained anaesthetist has always been available, no intravenous barbiturate was used, and all cases were given cyclopropane, oxygen and a relaxant with intubation, and this regime has achieved the low infant mortality rate of 0·4 per cent. Certain cases, such as profound toxaemia, require special mention. Local analgesia with thiopentone on opening the lower segment, has improved the infant's chances of survival. It is necessary to emphasize that in operative obstetrics the anaesthetist and obstetrician are members of a team.

Dr. E. G. Rees Jones: The report on confidential enquiries into maternal deaths in England and Wales during 1952–54 states that 49 deaths were due to complications of anaesthesia, and in a further 20 anaesthesia was a contributory factor. Of these deaths no fewer than 32 were due to inhalation of stomach contents. In a series of cases reported from New York, all patients showed pulse rates over 110 per minute, respiratory rates over 30 per minute and the majority developed cyanosis. Those patients who had aspirated semi-solid material developed obstructive signs and massive collapse leading to death.

The women who aspirated fluid contents developed signs of acute asthma. Experimental work on rabbits' lungs showed that tenth normal hydrochloric acid or unneutralized stomach contents could be responsible for these findings.

Gastric emptying may be delayed up to 48 hours in labour and it is, therefore, a false assumption that fluid diet in labour is safe. Further cases of this syndrome are now presented, and a different form of treatment based on the theory that the syndrome is due to intense broncho-constriction.

In the first case vomiting occurred, the anaesthetic was discontinued and the patient returned to consciousness, and Dr. Rees Jones was called. After Caesarean section, the patient's colour was poor and there was tachycardia. Bronchoscopy was, therefore, done and bile stained fluid recovered. Rales and rhonchi were heard all over the chest, and this was construed as a condition similar to acute asthma. Xylocaine 4 per cent, 12·5 ml. with 1 ml. 1 in 1,000 adrenaline, were introduced into the trachea and bronchi via an endotracheal tube, which resulted in gradual disappearance of the asthmatic sounds and general improvement.

Another patient, undergoing forceps delivery, first had a stomach tube passed, and was then anaesthetized without the use of an endotracheal tube. Bile stained fluid was later noticed trickling under the mask and immediately the pharynx was cleaned out. Though satisfactory at first, 2 hours later the patient's condition caused alarm. She was maroon in colour, dyspnoeic and had tachycardia. Again xylocaine and adrenalin were instilled into the bronchial tree following a second anaesthetic needed to introduce an endotracheal tube. Rales and rhonchi disappeared, but later there was pyrexia and evidence of pulmonary infection.

The third case presented similar features. In the fourth case vomiting took place after the initial thiopentone. Again xylocaine was instilled after further measures, to allow the passage of an endotracheal tube, but the results were not so satisfactory, and with Brockbank's work on asthma in mind an intravenous infusion of 100 mg. hydrocortisone in 5 per cent dextrose was run at moderate speed. In 15 minutes the patient's condition was satisfactory.

The fifth case showed over-enthusiastic therapy. The obstetric registrar had seen the success of xylocaine and used it himself, but convulsions resulted. Thiopentone 2 ml. controlled the convulsions, and oxygen improved the hypoxia. Soon the patient shouted in delirium and two further doses of thiopentone were needed to restore peace. The amount of xylocaine used was 30 ml.

In 1953 Platz reported cases of severe adrenal insufficiency resulting in maternal death. Other workers have demonstrated the presence of cortisone and hydrocortisone in placental extracts. It may be that the loss of the placenta with the inhalation of stomach contents causes a much more serious situation in pregnant women, than inhalation of stomach contents in other people.

In conclusion Dr. Rees Jones suggested methods of treatment to lessen anaesthetic deaths:

(1) Investigation into the needs of labouring women for food and fluids.

(2) The use of a cuffed endotracheal tube.

(3) If there is inhalation of stomach contents, bronchoscopy and instillation of xylocaine, followed by infusion of hydrocortisone if there is no improvement.

Discussion

Dr. J. L. Murray remarked that there had been little said about domiciliary anaesthetics. Complicated situations were met in the home, endotracheal tubes were impossible, and because of open fires one was limited to nitrous oxide, oxygen and trilene. What should the general practitioner be trained to use?

Mr. T. F. Redman supported Dr. Murray. He thought chloroform changing to ether and oxygen the safest, and felt coroners should overcome their fear of chloroform.

Dr. O. G. Bark thought that in general practice the only time a general anaesthetic was necessary was to remove a retained placenta. Chloroform was preferable to ether, and at one time residents at University College Hospital were taught to give chloroform for these cases.

Mr. L. Snaith said that in the past chloroform had long been used without trouble. Pregnant women behave differently from the non-pregnant, and in respect of chloroform behaviour may also be different.

Dr. M. O'Grady agreed that the occasional anaesthetist should use the technique he knew best. There were not enough cases to train everyone in the use of chloroform.

Dr. W. Calvert was sorry to see revived the myth that pregnant women were tolerant to chloroform. He had seen a maternal death during chloroform induction. Why were practitioners below the age of 50 reluctant to give an anaesthetic, and whose fault was it that there was no training?

Dr. L. A. Gifford gave advice about the use of simple methods. The head should be tipped to the right with a

pillow under the shoulder. In this way the lithotomy position can be maintained, and gravity keeps food away from the glottis.

Dr. I. C. Geddes mentioned that local anaesthetics were absorbed from the lung at the same speed as they can be given intravenously. Was xylocaine alone the effective agent, or the adrenaline?

Mr. G. W. Theobald remarked that the discussion was getting away from anaesthesia in difficult conditions, and as conditions were not ideal in 50 per cent of obstetric cases, what should be given? Pregnant women were not different in their tolerance of chloroform. Anaesthetists should teach simple methods which can safely be used by the house surgeon.

Professor C. S. Russell suggested use should be made of midget machines and a safe anaesthetic mixture devised which could be given in difficult anaesthetics.

Dr. M. Johnson said there was no simple safe technique with the existing drugs nor enough skilled anaesthetists. Fluothane had given a few bad risks. The industry was searching for a safe drug and trials of these had been made. One was a perfect analgesic, but about 15 per cent of patients remained fully orientated. Another drug produced a catatonic stupor but lack of co-operation. Nitrous oxide, chloroform and ether are all obsolete.

Dr. M. Swerdlow pointed out that anaesthetists would be out of business if the safe agent were found but this is impossible if depression of the cerebrum is needed. Training in the use of local analgesia should be given, and efforts made to find safe drugs to replace general anaesthetics if skilled help was not available.

Mr. B. Williams placed open ether first for a retained placenta. It was easy to put out the fire. Fluothane causes uncomfortable uterine relaxation. The main cause of death, vomiting, only occurs with complicated apparatus. Spinal analgesia resulted in little blood loss and was safe for the baby. No general anaesthetic contracts the uterus. Pregnant patients are more susceptible to spinal analgesia, postural hypotension occurs in the dorsal position and there is a risk of neurological damage, but in a recent review of 800 cases there had been no deaths or complications.

Professor T. N. A. Jeffcoate summarized the proceedings.

In this diverse discussion there had not been much difference of opinion between the anaesthetists and the obstetricians. There was need to relieve pain and provide comfort for the surgeon. Anaesthesia offers a danger to both mother and baby, though perhaps it is exaggerated, but as many risks disappear, anaesthetic risk becomes more prominent. With an expert and the drugs to which he is accustomed this risk is minimal. The obstetric field presents special problems—many anaesthetics are given by the inexperienced and often in difficult circumstances. Very good facilities may be almost as dangerous as very poor, and where an anaesthetist is present at all deliveries patients may be almost forced to have an anaesthetic. No matter what anaesthetic is chosen, an element of danger is introduced. The passage of the baby down the four inches of the birth canal is more dangerous than crossing the road, and no one does this anaesthetized. The scope of local analgesia has widened, but the more we use local analgesia the less opportunities there are to get the experience in general anaesthesia we expect.

Dr. Pooler, in conclusion, found two points emerged—firstly the aspiration problem, the main cause of death with general anaesthesia. Tipping with a pillow under the shoulder was a real contribution to reduce this risk.

Secondly, there was the problem of teaching residents. In answer to questions sent to general practitioners, 80 per cent would apply forceps in the home and 98 per cent would give an anaesthetic, yet 38 per cent of these practitioners had never had hospital experience. Dr. Pooler predicted that soon 50 per cent of practitioners would use local analgesia, and he asked if we should teach the technique of local analgesia or general anaesthesia. Obstetricians are all convinced what is the correct anaesthetic, but all want a different one.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

November 1958

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Liverpool on 21st November, 1958. The President, Dr. E. A. Gerrard, was in the Chair.

Miss U. M. Lister reported a case of

Recurrent Volvulus in Pregnancy

Volvulus is most frequently encountered early in the puerperium or in labour, when it presents difficulties both in diagnosis and in treatment. Should volvulus occur in the last 10 weeks of pregnancy, the difficulty in access makes resection of bowel hazardous, and if the bowel is still viable, reduction of the volvulus may then be justifiable.

The patient was sent up for the first time on 31st August, 1956, with the provisional diagnosis of hydramnios. She was a woman of 28 who thought herself pregnant for the 4th time, and due for her confinement towards the end of November. Her present pregnancy had progressed without mishap until the last 5 days. From then on attacks of colicky pain in the left loin increased in frequency despite regular defaecation. Abdominal distension had become apparent 4 days before, and increased rapidly during the last day with the cessation of the passage of flatus and the onset of vomiting.

Examination showed a pale, anxious woman, with a rapid pulse, acetone in the breath and a coated tongue. The abdomen was grossly enlarged with distended loops of bowel, showing peristalsis, but the foetus could not be detected. An X-ray of the abdomen showed the uterus containing a 30-week foetus displaced to the right, grossly distended loop of bowel but no fluid levels, and the point of rotation not clearly seen.

At laparotomy it was found that the descending and sigmoid colon had undergone 2½ turns in a clockwise direction, and, as the bowel was still viable, the obstruction was released, leaving resection of the redundant colon until after delivery. Recovery from operation was rapid.

Arrangements were made for delivery of the patient in hospital, and at the next four visits to the clinic all remained well. Some 2 weeks before term she was admitted to hospital as a precaution, though, apart from a lax abdominal wall allowing the uterus to lie obliquely to the right, there was no abnormality. Later bowel distension was detected and increased steadily despite defaecation, until after 8 days labour commenced and in 4½ hours a baby weighing 8 pounds 11 ounces was delivered.

By the 5th post-partum day the distension was so marked that laparotomy was again performed, and the pelvic colon was found distended due to a half-turn in a clockwise direction. The pelvic colon was resected and an end-to-end anastomosis of the descending colon to the recto-sigmoid junction performed. Recovery from the second operation was again uneventful.

If volvulus should occur in the last weeks of pregnancy, when access is difficult, reduction of the volvulus seems advisable, but thereby bringing a risk of recurrence at the more usual time near term.

Discussion

The President could only recollect one case of intermittent volvulus where right-sided pain led to confusion in the diagnosis.

Mr. N. L. Edwards thought the association of acute abdominal emergencies and pregnancy very serious and might form a suitable subject for discussion at some later date.

Mr. H. H. Francis had seen 3 cases of volvulus though not associated with pregnancy. Volvulus and intussusception were the only two causes of acute large bowel obstruction. He mentioned the value of X-ray in the early diagnosis of intestinal obstruction.

Mr. T. B. FitzGerald asked what were the reasons for resecting the loop of intestine when it was not gangrenous.

Mr. T. F. Redman had seen a case of subacute obstruction in the puerperium due to gross constipation which had been cured by an enema.

Mr. P. Malpas read a paper on

Pseudomyxoma Peritonei

(This article appears on page 247 of this issue)

Discussion

The President thanked Mr. Malpas for his thoughtful and beautifully presented paper.

Mr. N. L. Edwards had had experience of 2 cases which bore out the contention that the condition is malignant *ab initio*. The first was a woman of 40 undergoing hysterectomy for fibroids. Both ovaries were lightly adherent to the broad ligaments and a gelatinous exudate was seen. Later she returned with a hydrocele of the canal of Nuck which proved to be a pseudomyxoma, but it was not until 25 years after the initial operation that a pneumonectomy was performed. Pseudomyxoma peritonei was also found, and in the end she developed an intestinal obstruction from which she died. The condition seemed to start on the surface of the ovary.

The second patient had bilateral pseudomucinous cysts, both ruptured, and a mucocele of the appendix. She made a perfect recovery and was well 20 years later.

Mr. T. B. FitzGerald commented on the possible origin from mesodermal tissue and the resemblance to Wharton's jelly.

Dr. R. Newton had seen a number of cases under the care of the late Professor Dougal, on whom he had had to operate for the 3rd or 4th time. They were all ovarian in origin, but none had followed the rupture of a pseudomucinous cyst.

Mr. C. H. Walsh had removed a great deal of pseudomucin from a patient with normal ovaries but a mucocele of the appendix. Many years later she was still alive and well.

Professor T. N. A. Jeffcoate had seen only 1 case in 10 years. She was a post-menopausal woman with prolapse, discharge and a pyometra. On opening the pouch of Douglas pseudomucin poured out. When the abdomen was opened, the ovaries though covered with pseudomucin looked normal, and it seemed to be coming from the region of the caecum. The ovaries, when sectioned, were found to be covered by a thin layer of "cancerous" cells and it is from these that the pseudomyxoma was derived.

Members of the Society had seen 5 cases of pseudomyxoma peritonei in the last year, and at the Hospital for Women at Leeds there had been only 2 cases in the last 20 years.

In his reply Mr. Malpas said when a pseudomucinous cyst is ruptured and the fluid removed the condition does not recur and this is not pseudomyxoma peritonei. In 2 of his cases the tumour was a teratoma. It was difficult to say if the appendicular lesion was primary or secondary, and most patients with pseudomyxoma peritonei die eventually of intestinal obstruction.

Mr. C. J. Dewhurst read a paper on

Some Problems of Intersex

Basically our sex depends on the arrangement of our chromosomes. If this is XY testes and masculine genitalia develop, if XX ovaries and female genitalia, and this can be distinguished by the presence of sex chromatin in the nuclei. There are, however, other influences, genetic and endocrine, on sexual development, and if these act soon after the gonad has formed they can interfere with genital development resulting in a common form of intersex in which the gonadal and chromosomal sex is the same, but the sex as determined by the genitalia is in doubt. If these influences act at a very early stage

they can interfere with the development of the gonad with the result that (*a*) both ovarian and testicular tissue develop, (*b*) there is testicular tissue where there should be ovary or *vice versa*, and (*c*) gonadal tissue is absent. Since these combinations are possible, in a difficult case there is no substitute for complete examination including examination under anaesthesia and laparotomy, endocrine assay and assessment of sex chromatin. No single factor indicates in which sex the patient should best be brought up.

Usually we do not know the cause of the abnormality, and it is no longer active. Sometimes we know the cause, and the problem is how it may be corrected to allow the patient to assume the proper sex. Important causes are tumour or hyperplasia of the adrenal gland, and ovarian or pituitary tumour.

(1) (a) *Intra-uterine form of adreno-genital syndrome.* Excessive androgen production by the adrenal cortex gives rise to enlargement of the clitoris in girls, with excessive fusion of the labial folds to reduce the vaginal introitus to a tiny opening. Untreated, the condition progresses to precocious heterosexual development. A severe metabolic upset may also be associated. The cause of the abnormality is failure of the body to convert progesterone to cortisone, so that the production of A.C.T.H. is not inhibited, and adrenal cortical hyperplasia results. Treatment with cortisone gives good results, but the dosage must be carefully controlled and continued indefinitely. The diagnosis can be confirmed by the finding of raised 17-ketosteroid excretion level in a 24-hour specimen of urine, or by the response to cortisone therapy.

(b) *Adult form of adreno-genital syndrome.* Not all cases of adreno-genital syndrome have associated metabolic upset, and the patient may not be seen until later in life. Amenorrhoea, lack of breast development, increased hair growth on face and body and genital abnormalities with enlarged clitoris and narrow vagina, result. Diagnosis can be made by finding a raised 17-ketosteroid excretion or by treatment with cortisone.

The adreno-genital syndrome is the commonest form of female intersex. There had been another cause in a child whose mother developed an arrhenoblastoma during pregnancy.

(2) *Male Intersex*

Here there is seldom a recognizable cause, and the problem is how can the child best be brought up. An illustration was a "girl" of 8 with an enlarged clitoris. Examination showed her to be chromatin negative, to have a vagina, uterus, Fallopian tubes, and one intra-abdominal testis. As she was well adjusted to the female sex, no change was contemplated.

In the Testicular Feminization Syndrome the chief features are a normal female appearance except for absent axillary and pubic hair, infantile vulva and short blind vagina, intra-abdominal testes, and the skin sex is chromatin negative. Clearly these patients can only live as women, and it is doubtful if removal of the abdominal testes should be done since they probably produce oestrogens.

Cases in Which the Chromosomal and Gonadal Sex are Not the Same

(1) *Ovarian and testicular tissue both present.* The tissue may be separate or conjoined as ovotestes, differing genital abnormalities are often present, and it must be difficult to know what to do for the best. Functional possibilities of the external genitalia are as reasonable a basis for decision as any. If a gonad that is not homogeneous is found at laparotomy, biopsy should be taken from more than one part of the gland.

(2) *Absent gonadal tissue.* The majority of patients with "Gonadal Dysgenesis" (Turner's syndrome) are chromatin negative. The chief features are dwarfism, genital infantilism, more or less female appearance but absent gonads. Other associated faults—webbing of the neck, wide carrying angle of the arms, coarctation of the aorta and colour blindness occur. It is believed that sexual infantilism and the female appearance result from destruction of the testes at a very early stage. Dwarfism and other abnormalities are due to associated genetic faults. Their presence may not be essential and probably examples of this condition exist in which they are not present, perhaps especially so when ovarian failure occurs in someone who is chromatic positive.

(3) *Klinefelter's Syndrome*—a condition in which in apparently normal young men testicular tubal atrophy develops and subsequently eunuchoidism. The majority of these patients are surprisingly chromatin positive.

(4) *Ovarian tissue where there should be testicular tissue.* In January, 1958 such a case was described in Liverpool.

In the above scheme most of the principle forms of intersex have been included, but there are two additional points: it is now believed that not all these patients begin with sex chromosome arrangement XX or XY, and it is suggested that the testicular feminization syndrome may be XXY and that gonadal dysgenesis may be XO. Secondly normal development physically for either sex does not necessarily mean normal behaviour for this sex. A case of transvestism illustrated this point. The patient was a girl of 18 who had always believed herself to be male and worn male clothes whenever she had the opportunity. She had a liaison with another girl on a boy and girl friend basis, and marriage had been proposed and accepted on the assumption that physical examination would prove her to be a man. Transvestism may arise under three circumstances.

(*a*) Associated with sexual perversion as in fetishism.

(*b*) Again with a sexual background as in homosexuality.

(*c*) Genuine transvestism as here in which the patient truly believed that nature has made a ghastly mistake.

In conclusion it must be stressed that it is essential to perform a full examination and investigation, and assess the case in the light of what is found. There are no doubt other less clear-cut cases of intersex, and each case must be considered on its own merits. Except where evidence

is overwhelming it is generally unwise to contemplate a change of sex after the early age of 2 or 3 years.

Discussion

The President, after thanking Mr. Dewhurst, referred to Dr. Brentnall's case. He had seen the patient with a beard feeding her baby. An arrhenoblastoma developed during pregnancy, and at the time of Caesarean section the tumour was removed. She had since been delivered again by Caesarean section. The child was now 15 but had not yet been examined.

Professor Jeffcoate congratulated Mr. Dewhurst in presenting a very big subject. In transvestism we are up against the physical and psychological problem of intersex. At the moment the transvestites were not entitled to be made the sex they wish. Both ethically and legally the problem was difficult and Professor Jeffcoate found himself surrounded by them! The difficulty is that one is asked to remove normal tissue, and when this is refused they become most aggressive.

He mentioned 2 cases. In the first, a girl of 13, testes had been found at operation for bilateral herniae. The testes were returned to the abdomen, and the phallus was noticed to be enlarged. At the age of 20 she returned. The phallus was enlarged with a female type urethra, the vagina 1½ inches long and the voice breaking. She was chromatin positive. At laparotomy the gonads were removed, and no tubes or uterus found. Breast development was achieved with oestrogens so that she was turned into a presentable female with slight voice change.

Another girl of 15 who had noticed her voice broken for 1 year was found to have flat breasts, slight axillary and pubic hair, a large phallus and normal ketosteroid excretion. When examined under anaesthesia a normal urethra, hymen and vagina were found. The uterus measured 2 inches by sound. It was thought she would have testes because of the dimple on her chin, and her chromatin sex was male. Culdoscopy was followed by laparotomy when 2 tubes were found, on one side a testis was removed and on the other there was only a small strip of tissue. The phallus was also removed.

It is usually best to make these patients into what they appear to be externally, or what they want to be. Only once had he advised change of sex. As regards removal of testes, in cases where there is voice change, this should be done probably soon after puberty.

Mr. N. L. Edwards had a friend with a dimple chin who had a baby. He also had seen a gawky girl of 17 with primary amenorrhoea who talked in rather a masculine way. There was a phallus, the vagina was 3 inches long, and the small gonad was an undescended testis. With oestrogens she had developed into a presentable female and become interested in men. Hot flushes occurred when oestrogens were withdrawn, and now she had become a rather gross female hanging on the arm of her husband.

Dr. D. C. A. Bevis had consulted the Medical Defence Union about the implications of surgical treatment in a patient who was a nuclear male with a vagina 1½ inches long, and had been told operation was permitted.

Dr. S. Bender felt sympathy for the transvestites who could obtain treatment in Scandinavia. They had greater sexual drive than other intersex patients.

Dr. D. N. Menzies saw transvestism as a type of fugue. He thought that even after operation they would not be satisfied, or other troubles might develop. The child on cortisone therapy should have the dose increased if an operation was required.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

December 1958

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Manchester on Friday, 19th December, 1958. The President, Dr. E. A. Gerrard, was in the Chair.

Dr. Gerrard delivered the Presidential Address on

Some Aspects of Obstetrics in Animals

Dr. Gerrard's first example was the salmon, and he outlined the complicated life history of this fish, illustrating his remarks with a film of the salmon preparing a bed at the bottom of the River Dee to receive the eggs. He then described the birth of the elephant, and a film was shown of the breech delivery of a dolphin. Finally there was shown a very excellent film of the incubation and neonatal periods of the Emperor penguin.

Dr. J. W. Hunter (Manchester) thanked Dr. Gerrard for his most interesting address and for his care of the Society during his term as President. Mr. S. B. Herd (Liverpool), Mr. D. W. Currie (Leeds), Mr. H. J. Malkin (Sheffield) and Professor H. Harvey Even (Newcastle) added their thanks on behalf of the other centres.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

January 1959

The Annual General Meeting of the North of England Obstetrical and Gynaecological Society was held in Manchester on 16th January, 1959. The following were elected officers for 1959:

President—Mr. H. Agar.

Vice-Presidents—Mr. D. W. Currie (Leeds), Mr. S. B. Herd (Liverpool), Dr. E. A. Gerrard (Manchester), Mr. T. G. Robinson (Newcastle), Miss D. C. Bates (Sheffield).

Honorary Treasurer—Mr. T. B. FitzGerald.

Honorary General Secretary—Mr. J. B. Farquhar.

Honorary Reporting Secretary—Miss U. M. Lister.

Mr. Agar took over the Chair from the retiring President, Dr. Gerrard.

Dr. J. M. King reported a case of

Spontaneous Rupture of the Oesophagus Associated with Pregnancy

A certified feeble-minded patient, aged 34 years, who had had 3 previous normal pregnancies, was admitted in premature twin labour at the 36th week. A history was not easy, but her records showed that she was an epileptic on phenobarbitone, gr. 3 daily, and had had no fit for over a year. On two occasions investigations had been undertaken for haematemesis, but no ulcer found. Thereafter the patient had remained in good health until 2 days before admission when a small "coffee ground" vomit had been produced.

The cervix was fully dilated on admission, and the first twin, whose foetal heart could not be heard, was stillborn, and the second twin, weighing 4 pounds 13 ounces, was delivered normally and alive. The third stage was uncomplicated.

In the first 24 hours the patient's general condition was satisfactory apart from a copious thirst. After 36 hours she became restless, looked pale (haemoglobin 60 per cent), her pulse rose to 130 per minute and her blood pressure was 130/80 mm. Hg. No abnormal signs could be detected, and a physician who examined her was equally puzzled.

For the next 8 hours, during which a packed cell transfusion was begun, her condition, apart from thirst, remained the same. About 43 hours after delivery she suddenly collapsed, her blood pressure falling to 60/40 mm. Hg. Respiration rose to 36 per minute, numerous moist sounds were heard all over the chest, and there was upper abdominal distension and tenderness. Despite the blood transfusion, the patient died 2 hours later.

At post-mortem examination the outstanding feature was a longitudinal rupture 2 inches long in the anterior wall of the lower end of the oesophagus, surrounded by an area of early mediastinitis and communicating with both pleural cavities each of which contained about ½ pint of blackish fluid from the stomach. There was no ulceration in the alimentary canal.

Kennard (1950) reported a case of spontaneous oesophageal rupture in a primigravida of 37 who, after 5 days in labour, was delivered by forceps, developed a massive post-partum haemorrhage, and never regained consciousness following the anaesthetic. In 1946 Barrett described the first successful repair of a rupture of the oesophagus, and in 1956 he reported 22 cases of perforation of the oesophagus usually caused by an oesophagoscope or gastroscope. Avery Jones (1956) mentioned the possibility of haematemesis being due to a longitudinal laceration of the oesophagus, and Herd (1955) reported to this Society a case of status epilepticus in pregnancy, the patient dying 5 days later, when rupture of the oesophagus, stomach and diaphragm was found.

In this case it is possible, in view of the recent history of haematemesis, that there was an oesophageal laceration prior to labour which ruptured about 43 hours after delivery when her stomach was full of fluid. But one is left wondering what part, if any, pregnancy and labour played in the causation of this lesion.

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Discussion

In the discussion that followed the possibility of damage from a foreign body, previous scarring and increased vascularity associated with pregnancy were considered, also the more usual site of oesophageal trauma. There was, however, no sign of trauma, recent or old, though evidence of this had been sought.

FIFTEENTH BRITISH CONGRESS OF OBSTETRICS AND GYNAECOLOGY

CARDIFF

14th, 15th and 16th July, 1959

Applications for membership are still being received and those desirous of attending the Congress are advised to apply without delay to the Honorary Secretaries, Fifteenth British Congress of Obstetrics and Gynaecology, The Maternity Hospital, Glossop Terrace, Cardiff, from whom all particulars may be obtained.

HOSPITAL REPORTS

BY

JOHN S. TOMKINSON, M.B., F.R.C.S., M.R.C.O.G.

THE CLINICAL REPORT OF THE MATERNITY DEPARTMENT OF ST. MARY ABBOTS HOSPITAL FOR 1956

THE preface states that this is the first clinical report to be published since the Department was re-opened in this hospital in 1949. Fifty lying-in beds, twelve antenatal and six labour ward beds are available; as the demand for beds had increased, in 1956 cases were booked only on medical or social grounds. The number of deliveries increased from 309 in 1949 to 1,610 in 1956, but in the latter year the department was completely re-decorated so that 40 booked cases were delivered elsewhere. An analysis of figures gives a comparative table of results from 1949 to 1956 inclusive; out of a total of 9,754 deliveries, 2 maternal deaths occurred, one of acute yellow atrophy of the liver following one eclamptic fit and the other patient from heart failure (chronic rheumatic myocarditis) on the 4th day after delivery. The stillbirth rate per 1,000 total births varied between 9 and 19 and the neonatal death rate per 1,000 live births varied between 13 and 26.

In 1956 2 cases of eclampsia occurred, both in booked patients and in each case the fits were intra-partum, the mothers and babies surviving. The foetal mortality in uncomplicated breech deliveries was 13·7 per cent. A survey was carried out in the use of ergometrine (0·5 mg. with hyalase) with the birth of the anterior shoulder. In normal spontaneous vertex deliveries so treated the incidence of post-partum haemorrhage was 3·3 per cent; in similar deliveries without ergometrine having been given before the delivery of the placenta the incidence of post-partum haemorrhage was 10·0 per cent. The number of manual removals of the placenta was not materially affected, the report states, this incidence being 1·4 per cent. The forceps delivery was 4·25 per cent and the Caesarean section rate was also 4·25 per cent. Two cases of special interest are described, both of afibrinogenaemia.

THE MATERNITY REPORT OF KING'S COLLEGE HOSPITAL FOR 1955

THIS report follows the recommendations of the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists. There are no comments on the work of the year except for a statistical summary and the tables. There is no table of comparative statistics for previous years. A total of 818 patients were delivered; 2 maternal deaths occurred (one from acute pulmonary oedema following general anaesthesia considered due to sudden activity of a small phaeochromocytoma in the right suprarenal gland and the other from a lower nephron nephrosis, the patient also having amniotic debris in the lungs). The stillbirth rate per 1,000 total births was 22·3 and the neonatal death rate was 16·4 per 1,000 live births. The incidence of forceps delivery was 15·1 per cent and of Caesarean section 8·1 per cent.

Twenty-five cases of diabetes were delivered, 17 by Caesarean section and in 17 diabetics hydramnios occurred; 6 of the babies did not survive.

THE MATERNITY REPORT OF KING'S COLLEGE HOSPITAL FOR 1956

THE style of this report follows that for 1955. The number of patients delivered was 858 and no maternal death occurred. The stillbirth rate was 17·3 per 1,000 total births and the neonatal death rate was 23·4 per 1,000 live births. The incidence of forceps delivery was 16·72 per cent and of Caesarean section 9·9 per cent.

Forty cases of diabetes were delivered, 22 by Caesarean section; 5 of the diabetic patients had hydramnios and 5 of the babies did not survive.

THE FIRST CLINICAL REPORT OF THE PERIVALE MATERNITY HOSPITAL, WITH SUMMARIES FOR THE YEARS 1953–1957 AND DETAILED REPORTS FOR 1956 AND 1957

THIS is an interesting report, from the point of view of its presentation and also for the factual matter it contains. The back of the report consists of the tables recommended by the Standard Maternity Hospital Reports Committee of the Royal College of Obstetricians and Gynaecologists, but many of the tables are summaries and are often headed by a commentary which gives an account of the type of work performed. For instance, Table 28 (Surgical Induction of Labour) is preceded by

an explanation of the cases which were induced followed by the routine for induction of labour in primigravidae; Table 25 (Post-partum Haemorrhage) is headed by an account describing how in alternate weeks ergometrine 0·5 mg. with 1,000 units of hyaluronidase was given intramuscularly either with the crowning of the head or not until the conclusion of the third stage of labour. The incidence of post-partum haemorrhage using ergometrine in the second stage, in 1956 and 1957 was 1·9 per cent and 2·8 per cent whereas by using ergometrine in the third stage the incidence was 5·6 per cent and 4·0 per cent for the same years respectively.

The report contains an introduction which states the history of the hospital, the areas it serves, the types of patient admitted and the routine investigations carried out during pregnancy. The hospital has 52 beds, 110 patients were booked for delivery each month and during the five years 1953–1957 a total of 5,793 patients were delivered. The percentage of multiparae admitted rose each year to 64 in 1956 and 60 in 1957. The average forceps delivery rate was about 7 per cent and by using a pudendal nerve block 96 per cent of all forceps deliveries were conducted without a general anaesthetic. The Caesarean section rate was very constant during the five years, varying between 3 and 3·8 per cent. The stillbirth rate varied between 10·6 and 16·2 per 1,000 total births and the neonatal death rate between 5 and 15·1 per 1,000 live births. No maternal death has occurred in the hospital since 1950.

The hospital is to be congratulated on its work and for the conciseness and excellence of this report.

THE ANNUAL REPORT OF THE MILL ROAD MATERNITY HOSPITAL, LIVERPOOL, FOR 1957

This report consists of an obstetric section and a paediatric section. During 1957, a total of 3,272 patients were delivered; no maternal death occurred in the hospital but one booked patient in another hospital died from broncho-pneumonia with mitral stenosis. The perinatal mortality was 4·1 per cent (comprising a stillbirth rate of 2·4 per cent and a neonatal death rate of 1·7 per cent).

The first table shows comparable numerical data for the years 1952–1957 inclusive. The perinatal mortality rate in 1957 was the lowest during those six years. The incidence of ante-partum haemorrhage remained constant at about 3 per cent. The post-partum haemorrhage rate was 4·3 per cent and the frequency of manual removal of the placenta was 1·1 per cent; the report states that with greater use of local anaesthesia there has been a fall in the rate of manual removal of the placenta as many members of the resident medical staff favoured "elective" manual removal if the patient was already under a general anaesthetic. Breech presentation occurred in 4 per cent of deliveries with an overall perinatal mortality of 21·1 per cent (both these figures have remained fairly constant during the six years). The forceps delivery rate was 7 per cent, the same as in 1952; likewise the Caesarean section rate has varied only a fraction from 3·4 per cent.

The report is presented in an attractive manner, the tables following in general the scheme recommended by the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists but omitting the details of each case. Instead, comments are made about treatment and a fuller statistical analysis is given than is usual in Maternity Hospital reports. For instance, in Table 1, anaemia is defined as occurring when the haemoglobin level is below 70 per cent Haldane; the number occurring antenatally and postnatally is recorded, the treatment given and the comment that in the latter part of 1957 it became routine practice to prescribe folic acid for all patients requiring iron therapy in order to reduce laboratory investigations and to save a large number of patients the discomfort of marrow puncture.

Three cases of interest are described; the first being a patient who had had a lower segment Caesarean section performed in her first pregnancy following a trial of labour in which foetal distress occurred (she had a moderate degree of pelvic contraction), followed by two vaginal deliveries. In her 4th labour foetal distress was observed at full dilatation of the cervix and a manual rotation of an occipito-posterior was performed under general anaesthesia followed by a forceps delivery of a stillborn infant; the placenta was manually removed and a rupture of the uterus found. A laparotomy was performed, revealing that two-thirds of the Caesarean section scar had separated and also a 1½–2-inch laceration of the bladder, these injuries were sutured but the patient developed a utero-vesical fistula which was cured by subsequent total hysterectomy and closure of the fistula. The other two cases of interest comprised a case of mitral stenosis with aortic embolism and also a case of a cerebral vascular accident, both patients surviving.

The hospital is to be congratulated on presenting this report speedily and in a form which is easily assimilated. The provision of an index would be an advantage.

THE MEDICAL AND CLINICAL REPORT OF THE SIMPSON MEMORIAL MATERNITY PAVILION, ROYAL INFIRMARY, EDINBURGH, 1957

The introduction to this report states that experiments are still being tried with the object of improving the report and that no major alterations have been made. The report for 1956 was favourably reviewed and this report for 1957 is of an equally high standard for it has been published quickly and is presented in a way which is easy to read so that one gathers the facts and figures readily. The index is very helpful and a table of comparative statistics goes back to 1944. The obstetric section is 82 pages and the paediatric section 6 pages in length. For the most part the report does not follow the recommendations of the Standard Maternity Hospital Report Committee of the Royal College for the arrangement is different, comments are made about treatment

and results and for the most part detailed minutiae of cases are omitted with the exception of tables concerning eclampsia, multiple pregnancy, placenta praevia, breech deliveries, Caesarean section, vaginal delivery after Caesarean section or hysterotomy, stillbirths and neonatal deaths. There is a seven-page appendix of definitions which is helpful. Whilst this report shows those from other hospitals to be dull (and dilatory in publication) the Simpson Memorial Maternity Pavilion are fortunate in having as their Registrar of Records an obstetrician who is also an accountant.

There were 3,248 booked patients and 411 unbooked patients delivered after the 28th week of pregnancy. Two maternal deaths occurred in booked patients (from (*i*) eclampsia and (*ii*) mild hypertension with cerebral haemorrhage) and three maternal deaths in unbooked patients (from (*i*) severe eclampsia and severe antepartum haemorrhage, (*ii*) septic abortion, and (*iii*) infective hepatitis with acute necrosis of the liver). The overall stillbirth rate was 28·2 per 1,000 and the overall neonatal mortality was 25·1 per 1,000 viable births. The forceps rate was 16·4 per cent, a little above the average since 1944 and the Caesarean section rate 6·3 per cent, again above the average. The incidence of post-partum haemorrhage was 7·5 per cent and that for manual removal of the placenta 4·9 per cent. Nine cases of eclampsia were treated, all but two with bromethol; pre-eclampsia occurred in 10·6 per cent of patients, with a foetal mortality of 9·0 per cent.

THE CLINICAL REPORT OF THE MATERNITY DEPARTMENTS OF THE WINCHESTER GROUP HOSPITAL MANAGEMENT COMMITTEE FOR 1955

THE grand total of 1,680 patients were delivered by the four hospitals in this group. This was divided into the Royal Hampshire County Hospital 738, The Shrubbery Maternity Hospital, Basingstoke 434, Alton General Hospital 290 and the Andover War Memorial Hospital 218. No maternal death occurred.

The report follows the recommendations of the Standard Maternity Hospital Report Committee of the Royal College, some of the tables being summarized as a convenient economy. Most of the tables have a statistical summary at the head indicating how the work has been divided between the four units of the group. The preface to the report states that the booked cases of the Royal Hampshire County Hospital represent a selected midwifery practice, whereas the statistics for the Group as a whole approach those for an average cross-section of the rural population as it was responsible for two-thirds of the total deliveries in that area. The report does not contain an index, there is no table of comparative statistics and no cases of special interest are described.

The incidence of pre-eclampsia was 6·5 per cent in the Group, with a foetal mortality of 11·0 per cent. Post-partum haemorrhage occurred in 6·2 per cent of deliveries but a manual removal of the placenta was performed in only 0·7 per cent of deliveries throughout the Group. A forceps delivery was carried out in 6·0 per cent of labours and the Caesarean section rate was 2·8 per cent for the Group as a whole.

THE CLINICAL REPORT OF THE MATERNITY UNIT, WEST HILL HOSPITAL, DARTFORD, KENT, FOR 1956

THIS report commences with a preface which describes briefly the type of patient admitted, a summary of the year's work and a table of summarized results from 1952 to 1956. This is followed by the tables recommended by the Standard Maternity Hospital Report Committee of the Royal College. Two maternal deaths occurred during the year out of a total of 1,453 patients delivered; in one patient the cause of death was air embolism associated with Caesarean section and in the other patient death occurred 34 hours after a forceps delivery; this patient had had a laparotomy 15 hours before labour started for a twisted ovarian cyst. The report criticizes the management of this patient (she was not a booked case) because, although she had been told in early pregnancy she had an ovarian cyst, no action was taken; when she complained of abdominal pain at the 36th week of pregnancy no obstetrician was asked to see her and because a Caesarean section was not performed at the time of laparotomy. The cause of death was an intestinal ileus.

The stillbirth rate per 1,000 total births was 16 and the neonatal death rate was 19·4 per 1,000 live births. The forceps delivery rate was 6·3 per cent and the Caesarean section incidence was 4·9 per cent.

THE CLINICAL REPORT OF THE CRESSWELL MATERNITY HOSPITAL FOR 1954

THIS account of the activities during 1954 of the hospital follows the recommendations of the Reports Committee of the Royal College. No commentary and no table of comparative statistics is included. An introductory numerical summary shows that 1,508 patients were delivered, with 3 maternal deaths, all in booked patients. These deaths may be summarized as (*i*) a case of post-partum haemorrhage following severe pre-eclampsia and concealed accidental haemorrhage, subtotal hysterectomy and transfusion of 17 pints of blood and 3 pints of "Dextran" performed; (*ii*) secondary post-partum haemorrhage 12 days after delivery, a placental polyp removed under general anaesthesia, followed by further haemorrhage, uterine pack and then total hysterectomy (7 pints of blood transfused in all); (*iii*) spontaneous rupture of uterus, in a patient who had had one previous low forceps delivery in 1951. She had a forceps delivery

for foetal distress; the baby weighed 5 pounds. At post-mortem a tear 12 cm. long was found in the lower uterine segment. Four cases of special interest are described, one being of a patient who had aborted in 1952 and then in 1954 at the 25th week of pregnancy she developed a tender mass under an appendicectomy scar. This was explored and found to be two prongs of a hairpin projecting through the transversalis fascia and the peritoneum, the blunt end being fixed in the uterine wall one inch below the right round ligament. She was subsequently delivered of a live child.

The stillbirth rate was 28·5 per 1,000 births and the neonatal death rate 24·07 per 1,000 live births. The forceps rate was 7·7 per cent and the Caesarean section rate 3·0 per cent.

THE CLINICAL REPORT OF THE ROTUNDA HOSPITAL FROM 1ST NOVEMBER, 1956 TO 31ST OCTOBER, 1957

THIS report follows its usual style by commencing with a résumé of the year's work by the Master, followed by an account of the various departmental activities written by those in charge. Mention is made of staff changes, the type of work undertaken and of any advances made and about research projects in progress. This is followed by commentaries and statistical analyses under headings which are correlated with tables on the pattern recommended by the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists but omitting the detailed case particulars. Criticisms are made of their work and results. As has been said before, after reading this report one feels that one knows a great deal of the activities at the Rotunda.

A record number of deliveries, 4,474 occurred in the Intern Department. Contrasted with this, there was a further fall in the number of patients delivered in their homes by the Extern Department, the figure of 1,188 being about 500 less than in 1952–53. Cases delivered before the 28th week of pregnancy are included in these figures. In order to make a home confinement more attractive for patients, the Hospital District Service has been reorganized since 1st October, 1957, "to provide the patients with a very well covered medical and nursing service . . . very much higher than the patient is likely to obtain from a private nurse and practitioner".

Although seven maternal deaths occurred in the Intern Department, all were associated with severe medical or surgical conditions and in the opinion of the Master none was avoidable. No death occurred in the District Service. The stillbirth rate was 3·5 per cent in the Intern Department and the total infant mortality rate (deaths of infants born, excluding abortions, but including dead-born infants, stillbirths, etc.) was 4·91 per cent on the District Service; the combined stillbirth and neonatal death rate was only 22.

The incidence of toxaemia (all types) was 5·7 per cent against the total deliveries. Ten cases of eclampsia were encountered, all in booked cases and all but three patients had their fits after admission to hospital. The hospital has a toxaemia clinic for the special supervision of patients who have, or who are likely to develop, toxaemia. Only three of the eclamptics had attended this clinic. The post-partum haemorrhage rate was 1·5 per cent and that for manual removal of the placenta 2·6 per cent. The incidence of Caesarean section was about one per cent higher than during the past five years, being 4·9 per cent for the years under consideration; the forceps rate at 14·5 per cent was likewise higher than the average for the past five years (11 to 12 per cent).

This report is highly recommended; an evening spent studying it will be well rewarded, especially those interested in the production of maternity hospital reports.

BOOK REVIEWS

"Clinical Methods for the Analysis of Blood Coagulation. (Klinische Methoden der Blutgerinnungsanalyse.)" By PROF. DR. J. JÜRGENS, Frankfurt am Main and DOZ. DR. F. K. BELLER, Tübingen. Pp. xvii+391, with 104 figures. Georg Thieme Verlag, Stuttgart, 1959. Price D.M.56.

THE first chapter of this monograph is devoted to an exposition of the physiology of blood clotting. This is lucid and easily understood, as well as being comprehensive. Current theories are discussed and the authors have successfully attempted to achieve unity and coherence from the mass of facts available. One of the difficulties for the non-specialist, in understanding this subject, is the confused nomenclature. The authors have unravelled the tangle and included a useful table of synonyms.

The second chapter is devoted to classification and descriptions of the various clinical defects of blood coagulation. The pathological physiology of each condition is discussed and appropriate investigations and treatment are suggested. From the point of view of the obstetrician, the section dealing with coagulation defects associated with pregnancy is disappointingly short and summary (2 pages only). This is to some extent compensated for by the extensive list of references, which is a valuable feature of the whole monograph.

There is a useful summary of modern anticoagulant therapy and included are dosage schemes and details of the laboratory methods for the control of treatment. The use of Coumarin derivatives during pregnancy is condemned, as these drugs cross the placental barrier to affect the foetus. Heparin does not have this disadvantage. The remainder and major part of the book (256 pages) is devoted to detailed descriptions of apparatus and technical methods for the estimation of the various clotting factors.

This is a detailed, comprehensive and highly technical work and should become a standard textbook for the specialist in this subject. It is a useful reference volume for the practitioner who has to deal with these problems from time to time. The book is bound in a plastic cover, which should help to prolong its life on the laboratory bench.

Peter J. Huntingford

"The Year Book of Obstetrics and Gynaecology, 1958–1959." Edited by J. P. GREENHILL, B.S., M.D., F.A.C.S., F.I.C.S.(Hon.). Pp. 607, with 50 figures. The Year Book Publishers, Inc., Chicago and Interscience Publishers, Ltd., London, 1958. Price $7.50.

THIS book contains abstracts of articles relating to obstetrics and gynaecology, published in different medical journals throughout the world between July, 1957 and July, 1958. The selection of papers is naturally biassed in favour of the American literature. The distribution of the main abstracts according to the country in which they were published is as follows: America 261, Great Britain 37, Scandinavia 16, Germany 14, International 14, France 8, and 4 each from Asia, Canada, South Africa and Switzerland. In addition the editorial comments, which are most pertinent and valuable, refer to numerous other articles, some of which are also abstracted, but more briefly than those of the main text. The source of these short abstracts is more international. The subjects dealt with represent the current problems which are confronting obstetricians and gynaecologists all over the world. Conflicting points of view are fairly represented. The editor comments boldly and the reader is left in no doubt concerning his opinions.

Those who know this annual publication need no further recommendation. To those who have not met it before, this volume can be recommended as a worthwhile investment. Summarized in a short space are the results of recent research and current points of view. It is a gold mine of information and a valuable starting point in the search for references to particular subjects.

"Diseases of Women." By TEN TEACHERS under the direction of F. W. ROQUES. Pp. viii+556, with 211 illustrations. Tenth edition. Edward Arnold, London. 1959. Price 36*s*.

THE "Ten Teachers" textbook of gynaecology was first published in 1919, two years after the first appearance of the companion volume on midwifery, and both have long been favourites with successive generations of medical students. The 1959 edition of the gynaecological text is the tenth, and the list of former and present contributors reads like a Roll of Honour of our colleagues from the London teaching hospitals. Notable features of the new edition are the well-illustrated sections on vaginal and cervical cytology. Gynaecological endocrinology is pithily presented and the limitations of hormone therapy are judiciously assessed. The chapter on gynaecological tuberculosis has been rewritten, but the length of the initial course of drug treatment, 6–8 weeks, is less than optimum even if biopsy and other tests are negative at the end of that period. The chapters on prolapse and on gynaecological operations have also been recast, and in the latter happy judgment is shown of the amount of detail to be given in a textbook primarily for students. The section on vulvitis and vaginitis has been expanded but surprisingly the merits of nystatin in thrush infections have not been mentioned. As in previous editions there is a useful chapter on backache, and a wise one on psychosomatic aspects of gynaecology although it labours under the

somewhat old-fashioned title of "neurasthenia and neurosis in relation to pelvic disorders".

The illustrations are adequate and the text is easy to read, although the recommendation that, for vaginal examination, "a good light is essential and the bladder must be empty" is perhaps a more profound observation than intended! Altogether, the present director of this volume can be proud of having married tradition to progress with such felicitous result.

"Handbook of Obstetrics and Gynaecology for Nurses." By D. G. WILSON CLYNE, F.R.C.S.E., M.R.C.O.G. Pp. viii+204, with 53 illustrations. John Wright, Bristol. 1958. Price 15*s*.

THIS little book is intended for student nurses to cover the syllabus in obstetrics and gynaecology laid down by the British General Nursing Councils. The simplicity and brevity of the text are therefore to be accounted as virtues. Occasionally, however, the student might wish for a little more information, such as a simple definition of a hormone. A few statements are of doubtful validity —such as that more than 90 per cent of uterine cancers occur in the cervix, or that the ovum if not fertilized is cast out in the menstrual flow. And the statement that "the breasts are situated on both sides of the thorax" might have been put more exactly. Nevertheless these are minor blemishes in a handbook which not only the nurses but also their lecturers will find very useful.

EIGHTEENTH CONGRESS OF THE FEDERATION OF THE SOCIETIES OF GYNAECOLOGY AND OBSTETRICS OF THE FRENCH LANGUAGE

THIS Congress will be held on the 15th, 16th and 17th June, 1959, in the Faculty of Medicine of Paris.

PROGRAMME

15th June.	11 a.m.	"The Ovary Remaining after Hysterectomy"
	3 p.m.	Discussion
16th June.	10 a.m.	"Maternal Mortality During the Puerperium"
	3 p.m.	Discussion
17th June.		Communications

Further information from the Secretary-General, Dr. Maurice Robey, 4 Av. Saint-Honoré-d'Eylau, Paris, 16^{e}.

REVIEW OF CURRENT LITERATURE

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ANATOMY, PHYSIOLOGY

73. Innervation of the Human Vulva and Vagina: A Microscopic Study.

By K. E. KRANTZ. *Obstet. Gynec.*, **12**, 382–396. Oct. 1958. 21 figs. 70 refs.

This is an extensive and well-illustrated microscopic study of the sensory nerve endings of the human vulva and vagina. No nerve corpuscles were observed in the muscularis and mucosa of the vagina. Occasionally, free endings were observed in the mucosa and tunica propria. Ganglia and ganglion cells were present only in the adventitia of the vagina.

The pattern, shape and distribution of Merkel tactile discs, Pacini corpuscles, Dogiel-Krause corpuscles, and Ruffini corpuscles, free nerve endings, and peritrichial endings in the labia majora, labia minora, and clitoris were studied. Pacini corpuscles were found to be present within the epineurium of the large nerve bundles of the external genitalia.

J. G. Dumoulin

74. Contractions of the Human Fallopian Tube.

By S. N. UPADHYAY. *J. Obstet. Gynaec. India.*, **9**, 17–26. Sept. 1958. 1 fig. 10 refs.

An official drive to introduce family planning in the State of Behar, has made the excised Fallopian tube available for study in cases where the patient has been sterilized. The tube was excised, and half an inch taken from the uterine end was suspended in oxygenized Ringer Tyrode solution at 38° C. temperature. The fluid was constantly changed to remove tissue metabolites, and a kymographic recording was obtained of tubal movements.

During the oestrogenic phase of the menstrual cycle, at a time when proliferative endometrium was obtained on curettage, 17 tubes were removed. The tracings showed that both the amplitude and frequency of their contractions increased progressively till mid-cycle. Both amplitude and frequency were further increased by the introduction of ergometrine into the fluid at this time. When endometrial biopsy showed a secretory activity, the amplitude and frequency of the contractions diminished, and the increase produced by the introduction of ergometrine was very much less. Fifteen tubes removed at time of Caesarean section showed that movements tended to be generally diminished in comparison with those shown during the menstrual cycle. Ergometrine introduced at this time increased the amplitude greatly, but the frequency to a lesser extent. Twelve tubes were investigated in menopausal women at time of hysterectomy, when all contractility was feeble and irregular.

It is postulated that oestrogens are of primary importance in the production of tubal activity, and that other hormones play a lesser part in their initiation and maintenance. As the uterus is similar to the tube in development and structure, it is thought that the responses of the uterine musculature would closely resemble those of the Fallopian tube.

John McKiddie

75. The Living Human Ovum.

By L. B. SHETTLES. *Amer. J. Obstet. Gynec.*, **76**, 398–404. Aug. 1958. 24 figs. 3 refs.

In this beautifully illustrated article are described early human ova obtained by aspiration of follicles or irrigation of Fallopian tubes, and studied by phase contrast microscopy. At ovulation the ova were

surrounded by 3,000 to 4,000 corona radiata cells containing granules and connected to each other by intercellular tubes. From each of the cells near the zona pellucida a tubule extends into the perivitelline space and apparently a granular liquid is expelled from the tubule into the space, presumably to feed the ovum.

Within the Fallopian tube the zona pellucida in time becomes completely free of corona cells which allows easier passage of the ovum. Spermatozoa come into contact with the ovum by chance, and having once accidentally touched it become orientated at right angles to the zona pellucida which is surrounded by innumerable spermatozoa. More than one spermatozoon may penetrate the ovum. When the ovum is fertilized in the outer one-third of the tube the zona pellucida remains intact during the early stages of cleavage and expansion which occur during the passage through the tube, and it is still intact when the ovum reaches the uterine cavity. A two-cell stage developed *in vitro* after 29 hours and a morula 72 hours after exposure to spermatozoa. As the two polar bodies have the same haploid chromosomal constituency as the ovum nothing is seen which would prevent multiple pregnancy resulting from fertilization of one or more polar bodies in addition to the ovum, and this may explain certain types of twin pregnancy. Possibly, too, tubal pregnancy might result from premature release of the fertilized ovum through rupture of the zona pellucida during its passage along the tube.

F. J. Browne

76. **Cervical Tampon: Synchronous Test for Ovulation.**

By J. B. Doyle. *J. Amer. med. Ass.*, **167**, 1464–1469. July 19, 1958. 3 figs. 16 refs.

The author describes a test for ovulation based upon the increase of glucose in the cervical mucus during the ovulatory phase of the menstrual cycle. Donor inseminations have shown that the most successful results are achieved two or three days before the calculated time of the thermal shift (based upon the "square root sign" in the patient's basal morning temperature chart). The disadvantage therefore of relying upon temperature charts is that several days of maximal fertility have already elapsed before the trend of the curve can be recognized.

The new test consists of strips (Tes-Tape) impregnated with glucose oxidase. The strips are attached to the tip of a tampon which can be inserted by the patient herself. A positive test, indicating ovulation, is shown by a bright green colour on the strip. Two cases are described where it was possible to confirm that ovulation had occurred and that the glucose test was positive simultaneously in the cervical fluid and in the fluid aspirated from the peritoneal cavity during laparotomy.

It is suggested that this test gives a more accurate indication of ovulation than can be determined by temperature charts, and is therefore useful either for promoting pregnancy in infertile couples or for postponing it when this is desirable.

D. W. James

PREGNANCY

77. **Some Observations on the Histology of the Human Ovary During Pregnancy.**

By W. W. Nelson and R. R. Greene. *Amer. J. Obstet. Gynec.*, **76**, 66–90. July 1958. 7 tables. 14 figs. 23 refs.

A fluid filled central cavity was present in all but 3 of 19 early corpora lutea of pregnancy but in only 6 of 18 term or near term specimens. In the other 12 the cavity was filled by a loose mesenchyme-like connective tissue. There was considerable variation in the histological ageing of corpora lutea of equal menstrual age (counted from the first day of the last menstrual period) and a mesenchyme core replaced the central cavity in 3 specimens from 7, 8 and 13 weeks of pregnancy age. Theca lutein cells were not absent after the 5th month as is usually maintained, though few were present at the 8th and 9th months. Secretory granules were present in the granulosa-lutein and to a lesser extent in the theca-lutein cells, and the authors regard them as probably precursors of colloid material. Lipid droplets were also present in granulosa-lutein cells of early pregnancy but these were fewer at or near term.

Colloid was always present in the corpus luteum of early pregnancy but was scarce in late pregnancy. Calcium was absent in early pregnancy but was usually found in late specimens. For identification of a corpus luteum of pregnancy colloid and calcium are the most important intracellular inclusions, one or other being present in every corpus luteum of pregnancy, though colloid is far the most abundant. In shape and appearance a calcified globule can be described as a "clinker". It is probable that calcium is later absorbed as it is not found in corpora albicantia.

Corpus luteum cysts can be identified as being due to a co-existing pregnancy by the presence of colloid.

That continuation of follicle development extends through pregnancy is shown by the presence of developing follicles identical with those in any ovary, except for the addition of theca lutein reaction. Atretic follicles in various stages of atresia are also found, but do not differ from those in an ovary apart from pregnancy except for theca lutein reaction which gradually increases to become most marked at term. A decidual reaction was usually found in the cortex of the ovary though no direct correlation was shown with the duration of pregnancy.

The age of a corpus luteum can, by histological characteristics, be roughly correlated with the age of the foetus. By this means it is possible to distinguish an early from a late pregnancy, and one can even be reasonably certain in a further subdivision of very early specimens—from 1 to 3 months, but further than that it is not at present possible to go, just as definite dating of a corpus luteum of menstruation or of the endometrium to the exact day of the cycle is impracticable for most observers.

It is generally agreed that after very early pregnancy the corpus luteum is no longer required for the maintenance of pregnancy. Signs of degeneration are present from the beginning of pregnancy and are marked after

the 7th to 16th week. After the 4th month the corpus luteum appears inactive and changes little until the end of pregnancy though other evidences of activity become manifest in the ovary in the form of theca lutein and decidual reactions which must be attributed to placental hormones. Put in another way, in early pregnancy the ovary is an end organ which is stimulated by placental hormones. These are so efficient that after the third month of pregnancy the pituitary, both ovaries, and the adrenals could probably be removed without causing any apparent hormone deficit. *F. J. Browne*

78. **Hormones in Human Reproduction. Part II. Further Investigation of Steroid Metabolism in Human Pregnancy.**

By M. E. Davis and E. J. Plotz. *Amer. J. Obstet. Gynec.*, **76**, 939–953. Nov. 1958. 10 tables. 7 figs. 29 refs.

The authors had previously shown that cholesterol is available in corpus luteum and placenta for synthesis of progesterone, and Venning and Browne had demonstrated that while the kidneys are important in excretion of progesterone metabolites relatively small amounts of administered progesterone could be accounted for in the urine. Following the administration of tracer doses of progesterone, the present authors were able to recover 25 and 54 per cent respectively from the urine of 2 pregnant women, most of it within 24 to 48 hours after intramuscular injection. From the faeces 29 per cent was recovered, which shows that it is another important pathway of excretion in pregnancy. About 18 per cent was excreted in the breath. It is probable that the remainder is stored in the fat compartment for relatively long periods, whence it is gradually returned into the circulation. There was evidence too of an individual excretion pattern, and that absorption of progesterone from the site of an intramuscular injection is a fast and efficient process differing little if at all from that after intravenous injection.

When progesterone is given intravenously the plasma concentration of the hormone quickly declines and none is found in the plasma 24 hours later. This can be partly explained by its rapid inactivation to conjugated metabolites, and partly by diffusion into the fat compartments of the body where it is retained for a considerable time. These results demonstrate that erroneous conclusions may be drawn from values obtained for urinary metabolites such as pregnanediol as a measure of progesterone metabolism.

It was also demonstrated that oestrogens can be synthesized from cholesterol in human pregnancy, which supports the theory that this sterol is an important precursor of most if not all steroid hormones and that the metabolic pathway cholesterol-testosterone-oestrone is one of the routes of oestrogen biosynthesis in human pregnancy. Possibly androgens used for oestrogen synthesis within the placenta are produced by other sources such as the foetal adrenals or the ovaries and adrenals of the mother. *F. J. Browne*

79. **Electrolyte Balance Studies with the Antihormones.**

By A. C. Barnes and J. C. Buckingham. *Amer. J. Obstet. Gynec.*, **76**, 955–965. Nov. 1958. 11 figs. 11 refs.

The introduction of anti-aldosterone and anti-oestrogen offers opportunity to study electrolyte changes following suppression of these hormones. In the present study it was found that anti-aldosterone administered to normal pregnant women in the last month of pregnancy caused a negative sodium balance. In patients with pre-eclampsia it was much less effective, for while excretion of sodium and excess fluid was increased the patients still had a positive sodium balance, and there was no apparent effect on blood pressure or other aspects of the pre-eclamptic clinical syndrome. Possibly the dose was inadequate.

Administration of oestrogen antagonist to a menstruating or post-menopausal woman receiving oestrogenic supplements did not seem to have any influence in blocking the oestrogen effect on electrolyte excretion.

F. J. Browne

80. **Total Exchangeable Sodium and Potassium in Non-pregnant Women and in Normal and Pre-eclamptic Pregnancy.**

By I. MacGillivray and T. J. Buchanan. *Lancet*, **2**, 1090–1093. Nov. 22, 1958. 5 tables. 16 refs.

In many obstetric units the intake of sodium salts is restricted in the treatment of pre-eclampsia because of the belief that the oedema is associated with excessive retention of sodium. The authors describe the results of a study of sodium and potassium using the isotope-dilution technique. They found no significant difference in total exchangeable sodium between the non-pregnant and early-pregnancy values, nor between the normal late pregnancy and pre-eclampsia values. In late pregnancy whether normal or pre-eclamptic the amount of sodium was significantly increased, compared with non-pregnancy and early pregnancy. When the results were related to weight of the patient it was found that there was a decrease of body sodium per kilogramme in pre-eclampsia as compared with late normotensive pregnancy. There was no significant difference between mild and severe pre-eclampsia in either the total sodium content or the amount of sodium per kilogramme of body weight. There was a greater amount of potassium in late pregnancy compared with early pregnancy but there was no significant difference between the values in normal late pregnancy and pre-eclampsia. When the results were related to weight it was found that there was a decrease in the amount of potassium per kilogramme in pregnancy compared with non-pregnancy. As with sodium the difference between the normal late pregnancy and the pre-eclamptic groups was statistically significant. These findings confirm that there is storage of sodium in normal pregnancy and that there is a proportionate retention of sodium and water. There is also retention of sodium in pre-eclampsia but not greater than in normal pregnancy. If allowance is made for the excessive weight

increase in pre-eclamptics it is clear that these patients retain less sodium per kilogramme than those with normal pregnancy, probably because much of the increase in weight in pre-eclampsia is due to water retention. There is then no excessive storage of sodium in pre-eclampsia and water is stored without sodium. Retention of potassium also occurs in normal pregnancy but is less proportionately than might be expected when the patient's weight increase is taken into account. In pre-eclampsia the amount of total exchangeable potassium is approximately the same as in normal late pregnancy but the amount per body-weight is less, presumably owing to the greater water retention in pre-eclampsia.

H. H. Fouracre Barns

81. **The Urinary Excretion of Antidiuretic Substances by the Obstetric and Gynecologic Patient.**

By F. P. Zuspan, A. C. Barnes and J. R. Dillhoefer. *Amer. J. Obstet. Gynec.*, **76**, 619–625. Sept. 1958. 5 figs. 27 refs.

The tests were carried out on rats with extremely elaborate precautions to exclude other causes of antidiuresis such as stress of the test procedure, room temperature, urinary toxins and so on. It was found that pre-menstrual urine showed increased antidiuretic activity. The same was true of patients in the post-operative period, the amount of antidiuresis being proportional to the size and impact of the operative procedure and greater after abdominal than after vaginal surgery. In a single eclamptic patient antidiuretic substance was much increased, and it is suggested that it may be a factor in fluid retention and oliguria.

F. J. Browne

82. **Hyperemesis Gravidarum as a Possible Cause of Congenital Malformations.** (Hyperemesis gravidarum als mögliche exogene Ursache angeborener Missbildungen.)

By R. Mey. *Zbl. Gynäk.*, **80**, 1785–1791. Nov. 15, 1958. 2 tables. 15 refs.

If exogenous factors are responsible for congenital malformations, they are likely to act during early pregnancy. Studies of the early months of pregnancy carried out in retrospect in women who have given birth to malformed children may not yield reliable information.

The author investigated the outcome of pregnancy in 101 women who had been admitted for in-patient treatment of hyperemesis gravidarum before the 16th week. Three women miscarried subsequently. The remaining 98 patients had 6 children with congenital malformations (6·1 per cent): multiple haemangiomata, rachischisis, anencephaly, hare-lip and 2 cases of congenital heart disease. By contrast the general incidence of congenital malformations in the same clinic was 0·65 per cent. There was no history of hereditary factors in any of the 6 families concerned.

The author believes that teratogenetic effects of hyperemesis may be due to interference with oxidation processes.

Bruce Eton

83. **New Contributions to the Pathology of Cardiac Failure in Toxaemia of Pregnancy.** (Neue Beiträge zum Krankheitsbild der Herzinsuffizienz bei Schwangerschaftstoxämie.)

By G. Tarjan. *Zbl. Gynäk.*, **80**, 1772–1778. Nov. 8, 1958. 3 figs. 39 refs.

In this report, the author is concerned exclusively with those patients suffering from severe toxaemia of pregnancy and eclampsia who die from sudden myocardial failure. He points out that the morphological study of the myocardium in these cases has been neglected for no obvious reason, although most necropsy reports mention the flabbiness of the myocardium and dilatation of the right ventricle.

In the course of 12 years the author examined with fluorescent microscopy the organs of patients who died from toxaemia of pregnancy. In three such patients death had occurred from sudden cardiac failure. With fluorescent microscopy the presence of protein was demonstrated between the myocardial fibres. This protein had recently escaped from the circulation, separated the muscle fibres, destroyed their structure, and interfered with the function of the conducting system, embarrassing cardiac efficiency.

The sequence of events is thought to be arterial spasm leading to venous stasis and dilatation of the venules; if this condition persists endothelial damage permits the escape of proteins.

If circumscribed areas only are affected, regression and recovery is possible, but if the process is widespread, cardiac failure occurs.

Bruce Eton

84. **The Causes of Proteinuria in Toxaemia of Pregnancy.** (Über die Ursachen der Proteinurie bei Schwangerschaftstoxikosen.)

By V. Friedberg. *Zbl. Gynäk.*, **80**, 1930–1938. Dec. 6, 1958. 1 fig. 2 tables. 69 refs.

It has become clear in recent years that in healthy individuals the glomerular filtrate contains protein which amounts to about 5 per cent of the serum protein per hour. Only a very small fraction of this appears in the urine which means that most of it is reabsorbed by the tubules.

The author investigated the question whether proteinuria of pregnancy toxaemia is a sign of renal damage or whether there is a change in the capillary permeability throughout the body, revealed by oedema in the subcutaneous tissues and by proteinuria in the case of the kidneys.

He determined the varieties of proteins in serum, urine and oedema fluid by means of paper electrophoresis in 8 patients. There was a large measure of agreement in the protein fractions of the two capillary filtrates with a predominance of small molecular albumin.

The protein content in the glomerular filtrate was estimated by determination of the glomerular filtrate (inulin clearance) and by calculation of the so-called

albumin clearance after intravenous injection of 20 g. of albumin. Immediately following the injection there is a rise in albumin clearance and in the protein content of the glomerular filtrate, and an increase in albuminuria. This observation suggests that the albuminuria found in toxaemia of pregnancy is not due to diminished tubular reabsorption of protein, as the degree of proteinuria depends on the protein content of the glomerular filtrate.

The main conclusion is that albuminuria of pregnancy is a local renal manifestation of a generalized disturbance of capillary permeability.

Bruce Eton

85. Evaluation of Hypotensive Drug Therapy in Chronic Hypertensive Disease in Pregnancy.

By W. J. Dieckmann and J. P. Harrod. *Amer. J. Obstet. Gynec.*, **76,** 374–386. Aug. 1958. 6 tables. 8 figs. 11 refs.

Twenty patients with chronic hypertension were given hypotensive therapy which included protoveratrine A and B, apresoline and ganglion blocking drugs. Of the 20 women 14 left the hospital with live babies. In 1953 Dieckmann reported that only about one-third of women with chronic hypertension leave the hospital with live babies, hence it appeared that foetal survival was increased by 100 per cent. In the authors' opinion, however, this could be explained by better antenatal care and co-operation of the patients all of whom wanted a living child.

F. J. Browne

86. 30 Years of Eclampsia at the Gynaecological Clinic of the University of Graz. (30 Jahre Eklampsie an der Universitäts-Frauenklinik Graz.)

By E. Leinziger and F. Ribitsch. *Zbl. Gynäk.*, **80,** 1543–1548. Sept. 27, 1958. 3 figs. 4 tables. 5 refs.

In a study of the results of treatment in 335 cases of eclampsia which occurred between the years 1925 and 1954, the authors found that the maternal mortality was 39 per cent with conservative management, whereas it was 60 per cent with operative (abdominal or vaginal) delivery. The authors feel that the better figure for conservative treatment is misleading, because active treatment was used in the worst cases.

Amongst the different types of operative delivery, Caesarean section gave the best results for the child.

[As operative delivery was carried out in almost half the cases (159), a fair evaluation of such management should include details of the method of selection of the various types of treatment.]

Bruce Eton

87. An Evaluation of Chlorothiazide in the Treatment of Oedema in Pregnant Women.

By L. C. Chesley and L. Uichanco. *Amer. J. Obstet. Gynec.*, **76,** 467–472. Sept. 1958. 1 table. 2 figs. 7 refs.

Bed rest is one of the best diuretics in pregnant oedematous women and the clinician's assessment of the value of a diuretic drug is liable to be confused by the fact that the patient is simultaneously hospitalized and put on a low sodium diet.

In the present study the daily sodium intake and output were calculated during 6 days in hospital and on the low sodium regime. At the end of this time chlorothiazide was started, giving 1 g. daily equally divided between morning and evening doses and corresponding measurements continued. It was found that the maximum sodium excretion took place on the first day and that thereafter it became progressively less day by day. By the 6th day two of the patients were in positive balance, intake exceeding output. It is concluded that resistance to chlorothiazide develops within a few days; when the drug is restarted after about 3 days rest natriuresis is resumed as before.

F. J. Browne

88. The Supine Hypotensive Syndrome—A Factor in the Etiology of Abruptio Placentae.

By K. Smith and H. Fields. *Obstet. Gynec.*, **12,** 369–372. Oct. 1958. 14 refs.

The most widely accepted theory to explain abruptio placentae includes the association of hypertension with spasm and degeneration of the arterioles in the decidua basalis. This may explain toxic abruptio placentae but not the type associated with a normal blood pressure.

The authors believe that the non-toxic type of accidental haemorrhage results from rupture of the veins around the periphery of the placenta: and that this rupture is due to increased venous pressure caused by pressure of the flaccid uterus on the inferior vena cava. About 11 per cent of pregnant women develop hypotension on lying supine when not in labour. An example of the supine hypotensive syndrome initiating partial abruptio placentae by this mechanism is described.

J. G. Dumoulin

89. Experimental Abruptio Placentae: Histologic and Physiologic Studies.

By R. E. L. Nesbitt, Jr., S. R. Powers, Jr., A. Boba and A. Stein. *Obstet. Gynec.*, **12,** 359–368. Oct. 1958. 1 table. 17 figs. 7 refs.

Abruptio placentae was produced in 35 of 44 pregnancies in 6 adult mongrel dogs by ligation of the inferior vena cava. The kidneys showed acute tubular degeneration in all cases. In 3 dogs, renal blood flow was measured before and after vena caval ligation. Each showed a fall in renal blood flow which was interpreted as indicating an increase in renal vascular resistance.

Seven pregnant dogs subjected to ganglion block with trimethaphan camphorsulfonate (Arfonad) at the time of ligation demonstrated a reduced incidence of abruptio placentae when compared with the treated group. In all cases, the kidneys from this group of animals were clinically and histologically normal.

Arfonad will limit markedly the rise in venous pressure which occurs after venous occlusion. This raised venous pressure may be a factor in the aetiology of abruptio placentae and thus Arfonad might be used to prevent or modify the condition in humans. However, this is conjecture, and as yet the specific effects of the drug on a viable foetus are unknown. *J. G. Dumoulin*

90. **A Trial of Corticosteroid Therapy in the Prevention of Intra-uterine Death in Cases of Rhesus Incompatibility.** (Essai de la corticothérapie dans la prévention de la mort in utéro au cours d'incompatibilités sanguines foeto-maternelles du groupe Rh.)

By M. Lacomme, T. Boreau and C. Leconte des Floris. *Gynéc. Obstét.*, **57**, 237–243. 1958. 18 refs.

The authors treated, in Paris, 11 cases of rhesus incompatibility with prednisone during the pregnancy in an attempt to reduce the foetal loss *in utero*. They gave their first case in 1955 hydrocortisone and this case was most discouraging because the premature child, which was born spontaneously, at 32 weeks, died after 2 exchange transfusions and at autopsy was shown to have gross atrophy of the adrenal glands.

However, in 1956 the authors started treating a new series of patients with prednisone using the following dosages: from the 18th to 20th week of the pregnancy the patient was put in bed in hospital for four days and received during that time 25–30 mg. on the first day, 20–25 mg. on the second day, 15–20 mg. on the third day, and 10–15 mg. on the fourth day. She was then allowed to return home and continued on a maintenance dose of 5 mg. a day until delivery. Delivery was induced in each case at about the 34th week by low rupture of the membranes.

Each of the 10 patients watched had previously had a stillbirth or neonatal death due to rhesus incompatibility and in most cases of neonatal death, the babies had received exchange transfusions.

The corrected perinatal mortality for 8 of the 10 cases was 6 live children and 2 deaths. Two cases were dismissed because of extraneous factors. The authors insist that it is absolutely essential to carry out surgical induction about the 33rd to 34th week and exchange transfusion.

They only claim that it would be worth while for others to experiment along the same lines to see whether the perinatal mortality can be reduced in cases of rhesus incompatibility if corticosteroids are administered during the pregnancy *as well* as carrying out the usual procedures in cases of incompatibility. *Elliot Philipp*

91. **The Induction of Therapeutic Abortion by Means of a Hypertonic Glucose Solution Injected into the Amniotic Sac.**

By A. Brosset. *Acta obstet. gynec. scand.*, **37**, 519–525. 1958. 1 fig. 18 refs.

This is the description of a new method of "medical induction of therapeutic abortion" after the fourth month of pregnancy, by injecting a 50 per cent glucose solution into the amniotic sac by the abdominal route. After puncture of the amniotic sac as much as possible of the amniotic fluid is aspirated and a similar or slightly larger amount of the hypertonic glucose solution, to which 500 mg. of terramycin have been added, is injected.

Fifty-four patients have been treated by this method. In 51 of them abortion took place within 13 to 108 (average 38) hours of the injection; the other 3 patients missed abortion, and the uterus had to be evacuated surgically. There were no complications in the whole series.

[Although the actual induction is by means of an injection, this method cannot very well be described as "medical" as it is stated that ". . . abortion occurs. Curettage is then generally carried out . . ."]

N. Alders

92. **An Unusual Obstetric Case.**

By M. Segal. *S. Afr. med. J.*, **32**, 1164. Dec. 6, 1958.

The author describes a case in which menstruation commenced at the age of 33 years. This followed intermittent stilboestrol therapy over a period of 18 months. Laparotomy had been performed many years previously for an episode of abdominal pain, and it was then found that the patient had an infantile uterus, tubes and ? ovaries. At the age of 35 years she became pregnant and was delivered of a 2 pounds 6 ounces female infant.

L. J. Abramowitz

93. **Blood Volume and Anemia of Mother and Baby.**

By C. J. Lund and T. R. C. Sisson. *Amer. J. Obstet. Gynec.*, **76**, 1013–1023. Nov. 1958. 7 tables. 6 figs. 19 refs.

The accuracy of our common laboratory haemoglobin determinations and haematocrit depends on a constant relation between plasma and red cell volume but in pregnancy this is disturbed by blood dilution which varies much in amount even in normal pregnancy. The authors found that of healthy women at term 20 per cent had plasma volumes less than the average normal (hypovolaemia) and 20 per cent had hypervolaemia. A false impression of haemoglobin and red cell volume may therefore be gained if this is not taken into account. A more precise definition of anaemia should relate the total haemoglobin mass and red cell volume to the weight of the patient, the haemoglobin and red cell volume being stated in grams per kilogram and millilitres per kilogram of body weight respectively. The patient is not anaemic if the total haemoglobin mass is not less than 11·0 g. and the red cell volume below 29·0 ml. per kg. of body weight.

The haemoglobin and red cell volume of babies of anaemic mothers were significantly lower than those of normal mothers indicating that anaemia in the mother is often followed by anaemia in the newborn.

F. J. Browne

94. Measurements of Placental Function.

By E. S. Taylor, P. D. Bruns, H. J. Hepner and V. E. Drose. *Amer. J. Obstet. Gynec.*, **76**, 983–993. Nov. 1958. 7 tables. 3 figs. 22 refs.

This is a report of experience in measurement of placental function by determining levels of excreted oestrogens and sodium pregnanediol in the urine of 57 pregnant women, and by measurement of radioactive sodium clearance from the myometrium during the last 20 weeks of gestation.

The authors concluded that a low level of oestrogen excretion is not significant if the pregnancy is proceeding normally and that pregnanediol estimations are not helpful. Prolonged sodium clearance (over 6 minutes) was found in 23 normal cases and in 77 per cent of pathological pregnancies. The abnormalities include pre-eclampsia, chronic hypertension, maternal infection, oedema, twins and 2 cases of postmaturity in one of which the infant showed signs of chronic anoxia and in the other did not. In their diabetic cases the clearance was normal.

F. J. Browne

95. Plasma Cells in an Immature Human Placenta.

By K. Benirschke and G. L. Bourne. *Obstet. Gynec.*, **12**, 495–503. Nov. 1958. 4 figs. 11 refs.

It has been suggested that plasma cells are the principal cell type responsible for the production of antibodies. The human placenta does not normally contain plasma cells. The only cells present in the placenta which could be confused with plasma cells are the Hofbauer cells whose function is not understood.

The authors found plasma cells in a few selected villi of an immature placenta (29 weeks gestation) around a large intervillous thrombus, and nowhere else in the placenta. They examined 10 placentae with chorion-amnionitis and known bacterial infection, but none showed plasma cells; nor are these cells found in syphilitic, tuberculous or virus-infected placentae.

They believe that the plasma cells found may be formed from Hofbauer cells as the result of some specific stimulus, in this case the mass of maternal leucocytes in the intervillous thrombus.

J. G. Dumoulin

96. Studies of Cholinesterase Activity. IV. Liver Function in Pregnancy: Values of Certain Standard Liver Function Tests in Normal Pregnancy.

By H. J. Wetstone, R. V. LaMotta, L. Middlebrook, R. Tennant and B. V. White. *Amer. J. Obstet. Gynec.*, **76**, 480–489. Sept. 1958. 12 tables. 36 refs.

Serum total cholesterol was found to be increased in normal pregnancy and reached its peak at the time of labour when it might be as high as 550 mg. per cent (normal range 150–300 mg. per 100 ml.). Serum alkaline phosphatase activity rose in the last three months of pregnancy and reached its peak during labour when nearly 75 per cent had values in excess of the normal range of 5·0 Bodansky units. There was a fall of about 1 g. per cent in total serum protein from the first to the third trimester. A decrease of albumin accounted for two-thirds of the fall and of globulin for the remainder. Serum thymol turbidity, serum bilirubin, and serum cephalin-cholesterol flocculation were all normal. Serum cholinesterase activity was abnormally low as early as the first trimester and the fall continued till the third trimester when the mean value was 149 units compared with 160 units in the second trimester.

These findings are helpful in evaluation of possible hepatic disease in pregnancy. Thus a slight rise in alkaline phosphatase is of no significance and values as high as 10 to 15 Bodansky units may be seen without liver disease. On the other hand it seems clear that rise in bilirubin in pregnancy must be considered abnormal. Elevation of thymol turbidity or cephalin flocculation in the range of 3 to 4 plus in 48 hours is abnormal in pregnancy. Cholinesterase levels of non-pregnant women have been of great value in following the course of hepatic disease but in pregnant women low serum cholinesterase levels are normal and the enzyme test is therefore of little value in the study of liver disease in pregnancy.

F. J. Browne

97. Diabetes Mellitus and Pregnancy (1932–1957). An Analysis of the Factors Responsible for the Improved Fetal Salvage During the Current Decade.

By P. Pedowitz and E. L. Shlevin. *Amer. J. Obstet. Gynec.*, **76**, 417–424. Aug. 1958. 10 tables. 11 refs.

In the years 1932 to 1949 the foetal mortality in 141 viable pregnancies was 22 per cent; in the period 1950–1957 it was 8·7 per cent in 219 viable pregnancies. These improved results are put down to meticulous antenatal care with earlier recognition and prompt treatment of ketosis and pre-eclampsia. As a result of daily testing of the urine for acetone by the patient it is rare today to encounter clinical keto-acidosis unless the patient fails to co-operate.

Because of the high foetal mortality in toxaemia in the earlier series it was decided to terminate pregnancy within 72 hours after recognition of pre-eclampsia if the foetus was viable, and in the 36 cases so treated only one foetus was lost. All the foetal deaths in the earlier series occurred while the patient was being treated expectantly.

Another factor in lowering foetal mortality was delivery of all cases before the 38th week. Because it causes a high neonatal death rate delivery should not be effected before the 36th week unless there is complicating pre-eclampsia, progressive or repeated bouts of acidosis, or some other complication calling for immediate delivery. No categorical statement can be made as to the mode of delivery; if induction of labour and vaginal delivery is feasible it should be utilized, otherwise Caesarean section should be performed, and in the 1950 to 1957 series 65 per cent were so delivered. Breech cases are usually best treated by Caesarean section. Slightly more than one-third of the primary sections were done for an unfavourable cervix, more than half the remainder

because of a previous foetal loss or traumatic delivery, and the rest for obstetrical indications.

Unexplained intra-uterine deaths, recurrent episodes of pre-eclampsia, excessive size of infant, habitual abortion and glycosuria should lead one to suspect diabetes. Here post-prandial blood sugar and urine tests are likely to be more informative, as fasting specimens may show no abnormality. *F. J. Browne*

98. **Studies on Human Reproduction. II. The Influence of Diabetes Mellitus in Men Upon Reproduction.**

By A. RUBIN. *Amer. J. Obstet. Gynec.*, **76**, 25–29. July 1958. 4 tables. 10 refs.

In this study of married diabetic men and controls it was shown that 25 per cent of the diabetic men in the age group 30 to 34 were impotent. The frequency of impotence increased with age so that in the 50–54 age group it was 54 per cent. The incidence of abortion among the wives of the diabetic men was significantly higher than among the wives of controls, i.e., 17 and 10 per cent respectively. There was no difference in the birth weights of the offspring or in the incidence of stillbirths or malformations. *F. J. Browne*

99. **The "Pre-Diabetic" Period from an Obstetric Point of View.**

By L. HAGBARD. *Acta obstet. gynec. scand.*, **37**, 497–518. 1958. 8 figs. 44 refs.

In this paper from Gothenburg, Sweden, 274 pregnancies in 113 women who subsequently developed diabetes mellitus were analyzed. In all these women the disease developed during their child-bearing years, and in the majority before the age of 40. The incidence of abortion in the whole series was not increased. There was an incidence of 26·7 per cent (normally 1 to 2 per cent) of over-sized babies (birth weight over 4,500 g.). The perinatal mortality was high during the 5 years preceding the diagnosis of diabetes; in the 2 years before the diagnosis the perinatal mortality was as high as 37·3 per cent. Spontaneous premature labour occurred before the 37th week in 17·4 per cent of the cases, and during the last 2 years before the diagnosis 26·2 per cent of the deliveries occurred before the end of the 37th week. Four per cent (against 1·7 per cent in a normal control series) of the children of these "pre-diabetic" mothers showed congenital deformities.

Glucose tolerance tests were done on women who had given birth to children weighing more than 4,500 g., and on women with a history of severely deformed or stillborn children in whom there was no obvious obstetric cause. Altogether 189 women were examined in this way on the 4th or 7th day after delivery. It was found that the average level of blood-sugar both 60 and 90 minutes after administration of glucose was significantly higher in the test series than in a control series of 100 women.

In the author's opinion, the high incidence of foetal complications during the "pre-diabetic" period is due to the fact that some of the mothers had transient unrecognized diabetes mellitus during pregnancy, or at any rate had a lowered carbohydrate tolerance several years before the disease was manifest. It is, therefore, not correct to use the term "pre-diabetic" state.

N. Alders

100. **The Effect of Asian Influenza on Pregnancy.**

By L. J. ABRAMOWITZ. *S. Afr. med. J.*, **32**, 1155–1156. Nov. 29, 1958. 5 tables. 2 refs.

The effects on pregnancy of Asian influenza, as it occurred in Cape Town in August and September, 1957 were studied. Particular attention was paid to abortions, prematurity, stillbirth and neonatal death rates and the incidence of accidental haemorrhage. From the evidence available the effects were negligible.

Author's Abstract

LABOUR

101. **Rapid Delivery. Biological Action of Thiamine (Vitamin B_1) on Muscle Fibres of the Pregnant Uterus.** (L'accouchement rapide. L'action biologique de la thiamine (Vitamin B_1) sur la fibre musculaire de l'utérus gravide.)

By B. TRIANTAFILLOPOULO. *Gynéc. Obstét.*, **57**, 313–326. 1958. 80 refs.

The author makes a claim that thiamin, given in daily doses of 15 to 20 mg. a day throughout the pregnancy and by intramuscular injection of 100 mg. at the onset of labour, causes a marked acceleration of the labour process.

[The paper, however, to my mind is invalidated by the fact that each case received 2·5 units of pituitary oxytocic drugs. The claim is that the thiamin potentiates the action of posterior pituitary oxytocin. Since the oxytocin is always given after labour has been established, the procedure described in the article sounds rather dangerous. The argument, however, is impressive that there is a deficiency of thiamin in some women going into labour.] *Elliot Philipp*

102. **Alterations in Cardiovascular Physiology During Labor.**

By J. Q. ADAMS and A. M. ALEXANDER, JR. *Obstet. Gynec.*, **12**, 542–549. Nov. 1958. 3 tables. 2 figs. 7 refs.

The authors measured the cardiac output in labour by 2 injections at 3–6 minute intervals of a known amount of Evans blue dye and collection of blood samples from the femoral artery. Forty-one normal patients were studied in labour.

A rise in cardiac output accompanying each uterine contraction was found, amounting to 20 per cent over the output with the uterus relaxed. A proportionate rise in the heart rate was found. These rises were probably a response to pain, anxiety, and muscular activity, and the

squeezing of blood from uterine sinuses. There is also a rise in blood pressure during a uterine contraction.

Immediately after delivery of the foetus and placenta, the cardiac output is 18 per cent higher than upon completion of the first stage of labour. This is accomplished by an increase in stroke volume, the primary mechanism of increasing the cardiac output being the increased venous return. *J. G. Dumoulin*

103. Oestrogen and Progesterone Levels in Foetal and Maternal Plasma at Parturition.

By E. H. Aitken, J. R. K. Preedy, B. Eton and R. V. Short. *Lancet*, **2**, 1096–1099. Nov. 22, 1958. 2 tables. 33 refs.

Twenty-nine pregnant patients were studied and divided into 2 groups—one undergoing elective Caesarean section (14 cases) and the other normal labour (15 cases). All patients were in good health at the time of the studies. Maternal blood was collected from the cubital vein and foetal blood from the placental end of the cut umbilical cord. The time interval between these 2 collections was 5–10 minutes for the group when delivery was by Caesarean section and 0–22 hours in the other group. No significant difference was observed between the mean levels of any of the hormones in the maternal blood when Caesarean section samples were compared with those taken during normal labour. But in both groups there was a significant difference between the mean levels of oestrone, oestradiol-17β, oestriol and progesterone in maternal as opposed to foetal plasma. The oestrone and oestradiol-17β levels were lower in foetal than maternal plasma, but the oestriol and progesterone levels were considerably higher in the foetal plasma. The authors conclude that labour is not associated with any major alteration in the plasma concentrations of these hormones. *H. H. Fouracre Barns*

104. Excretion of Pregnanediol and 17-Hydroxy-corticosteroid During and After Labour. (Vergleichende Untersuchungen über die Pregnandiol und 17-Hydroxy-kortikosteroid-Ausscheidung während und nach der Geburt.)

By F. Cekon and H. Ehrlich. *Zbl. Gynäk.*, **80**, 1851–1862. Nov. 22, 1958. 4 tables. 55 refs.

The authors report the results of estimating the rate of excretion of pregnanediol (P.) and 17-hydroxy-corticosteroid (17-K.) in 25 patients.

P. was determined by the authors' own method (based on that of Astwood and Jones, Talbot, Sommerville and their co-workers). Estimation of 17-K. was carried out according to a modification of the method of Zimmermann.

As regards P., excretion on the day of labour showed a wide range between 1·7 and 14·7 mg. per 24 hours, but most figures varied between 3 and 10 mg. During the puerperium excretion values dropped steadily to less than 0·5 mg. by the 7th day.

17-K. excretion ranged between 7·8 and 23 mg. per 24 hours on the day of labour. This represents an increase by about 50 per cent above the values found in mature non-pregnant women (8–10 mg.). The high excretion rate continued for about 7 days after delivery in 15 out of 22 patients in whom the estimations were made. These large amounts are interpreted as a sign of an adaptation syndrome in pregnancy. As the high values persist after delivery, it would seem that the placenta is not an important source of 17-K. production. *Bruce Eton*

105. Cardiovascular Reactions to Pitocin.

By J. R. Reinberger and W. F. Mackey. *Amer. J. Obstet. Gynec.*, **76**, 288–291. Aug. 1958. 12 refs.

The authors' use of pitocin for induction of labour and control of post-partum haemorrhage has produced both mild and severe reactions, and they report a case of coronary spasm following its use in Caesarean section under spinal anaesthesia in a normal woman. After removal of the baby pitocin, 1 ml., was injected into the muscle of the uterus. The patient immediately complained of severe pain in the chest, associated with shortness of breath and a rise in the pulse rate from 85 to 120 per minute, which lasted 20 minutes. An electrocardiogram 3 hours after operation showed coronary spasm. They have now discontinued the injection of pitocin or any drug into the uterus at Caesarean section. They also cite 3 cases of tetanic uterus and foetal distress necessitating immediate Caesarean section and 3 cases of rupture of the uterus, all following intravenous pitocin drip.

F. J. Browne

106. Inhibitory Action of Halothane on Contractility of Human Pregnant Uterus.

By M. P. Embrey, W. J. Garrett and D. L. Pryer. *Lancet*, **2**, 1093–1094. Nov. 22, 1958. 1 table. 2 figs. 8 refs.

The authors record their investigation of the effect of halothane ("Fluothane") anaesthesia on uterine contractility by tocographic means. Studies were undertaken in 12 patients. In each case the pattern of uterine contractility was studied for a control period both before and after the induction of anaesthesia. The duration of anaesthesia varied between 13 and 35 minutes. In each of the 12 cases, halothane was found to have a definite inhibitory effect on the contractility of the uterus with complete or almost complete obliteration of the contractions. The inhibitory effect occurred rapidly after the loss of consciousness and disappeared just as quickly when the anaesthetic was withdrawn. The effect was also observed when an oxytocic intravenous infusion was also being given in one patient. *H. H. Fouracre Barns*

107. Graphic Recording of Movements of the Cervix during Labour. (Zur Frage der graphischen Registrierung von Kontraktionen des Muttermundes unter der Geburt.)

By H. NOACK and E. BLASCHKOWSKI. *Zbl. Gynäk.*, **80**, 1609–1616. Oct. 11, 1958. 7 figs. 22 refs.

The authors recorded simultaneously contractions and relaxations of the uterine corpus and cervix. Activity of the corpus was recorded with an external tocodynamometer; that of the cervix by means of a small balloon fitted between two plates above and below the cervix. Cervical pressure changes in the balloon were transmitted to a kymographic recording apparatus.

Records obtained from a few patients showed that normally each contraction of the corpus precedes by a few seconds relaxation of the cervix with a deflection of corresponding amplitude. Occasionally contractions of the corpus are not accompanied by any cervical relaxation.

Attempts to produce a spasm of the cervix by means of 1·5 units of posterior pituitary extract failed.

Bruce Eton

108. **Effect of Relaxin on Normal Labour.**

By L. V. DILL and J. CHANATRY. *J. Amer. med. Ass.*, **167**, 1910–1912. Aug. 17, 1958. 2 figs. 8 refs.

Relaxin is a water soluble substance extracted from the corpus luteum, and from time to time has been reported to be of value in facilitating dilatation of the cervix and reducing the length of labour. The authors have investigated this reported action by comparing the effects of two preparations of relaxin with a placebo. They observed the results in 47 patients, unselected except for the following criteria: (1) the absence of medical or obstetric complications; (2) the patient would have entered hospital before the cervix had progressed to 5 cm. in dilatation; (3) the engaged vertex would be presenting. Twenty-four patients were primiparas and 23 were multiparas and in all three groups the preparation was given by slow intravenous infusion.

Comparison was made as to the duration of labour, the degree of softening of the cervix, and other possible effects. Within the limits of this experiment it was not possible to demonstrate the value of relaxin. The authors have also tried relaxin in several cases of prolonged labour, hard cervices, and irregular uterine action, but no real effect has been recognized.

D. W. James

109. **Repository Tubocurarine in Obstetrics.**

By T. A. FRENCH. *Obstet. Gynec.*, **12**, 550–555. Nov. 1958. 4 tables. 17 refs.

Tubadil, a preparation of pure crystalline tubocurarine in a repository menstruum, was developed to provide muscle relaxation prolonged over 12 hours. It was used in 164 patients in labour, being administered intragluteally in doses up to 2 ml.

The author claims that it relaxes the patient physically and emotionally. It decreases pain from stretching of the perineum by the foetal head. It facilitates spontaneous and forceps deliveries, permits less extensive episiotomies and provides easier induction of anaesthesia. It does not cause respiratory difficulties in mother or babies.

J. G. Dumoulin

110. **The Significance of the Unengaged Vertex in a Nullipara at 38 Weeks Gestation.**

By L. BURKE, H. W. RUBIN and A. L. BERENBERG. *Amer. J. Obstet. Gynec.*, **76**, 132–136. July 1958. 4 tables. 7 refs.

In 250 consecutive primigravidae at 38 weeks the vertex was engaged in 195 and unengaged in 55 (22 per cent). Of the latter group engagement occurred in 44 at onset of labour. Thus at onset of labour the head was not engaged in 11 (4 per cent). In these cases the android pelvis predominated.

Of the women in whom engagement had occurred at 38 weeks 96 per cent had a normal delivery and 2 had Caesarean section, one for inertia, the other for elderly primiparity after 2 hours in labour. In the patients in whom engagement only occurred at start of labour, 95 per cent had normal delivery and 2 were delivered by mid-forceps. Of those without engagement at onset of labour 64 per cent had normal delivery and 4 cases came to Caesarean section, 3 for contracted pelvis and one for inertia.

From this it is apparent that if a head is engaged at the onset of labour there is a 95 per cent chance of a normal delivery and a 4 per cent chance of mid-forceps delivery. If it is not engaged at the start of labour Caesarean section will probably be required in one-third of the cases.

F. J. Browne

111. **Moulding of the Foetal Head During Normal Labour and in Contracted Pelvis.** (Die Umformung des kindlichen Kopfes während normaler Entbindung in regelrechter Hinterhauptslage und bei engem Becken.)

By U. BORELL and I. FERNSTRÖM. *Geburtsh. u. Frauenheilk.*, **18**, 1156–1167. Sept.; 1245–1256, Oct. 1958. 2 tables. 13 figs. 11 refs.

A radiographic study of moulding of the foetal head during labour was made at the Karolinska Institute, Stockholm. Antero-posterior and lateral X-rays of the pelvis were taken during labour as the head descended in 18 primigravid and 9 multiparous patients. They were all delivered spontaneously at full term with the occiput anterior. The babies weighed between 2,750 and 4,730 g. In all cases the pelvic measurements were adequate. Labour lasted from 2–24 hours, except in 1 patient who laboured for 40 hours. The films showed that in every case moulding occurred to a greater or lesser extent, and it was always of the same type. True overlapping of the cranial bones was never seen. The lower parts of the parietal bones were displaced inwards and upwards at the temporal sutures. The upper parts of the parietal bones rotated outwards and were displaced upwards. This resulted in an increase of the biparietal

diameter and the greatest increase measured was 10 mm. The sagittal suture was elevated relative to the base of the skull. The occipital and frontal bones were displaced inwards so that the occipito-frontal diameter was reduced (the biggest reduction measured was 8 mm.). Moulding was observed to occur as the head passed through the brim of the pelvis and the maximum degree of moulding was seen when the head was in the cavity with the lowest part between the ischial spines and the ischial tuberosities. Moulding disappeared completely when the head passed through the outlet of the bony pelvis. In several cases X-rays were taken as the head was crowned and the same pattern of moulding was seen as the head passed through the vulval ring.

Measurements were made of the displacement between the occipital and parietal and between the frontal and parietal bones at the lambdoidal and coronal sutures respectively. These measurements showed that the degree of moulding was related to the duration of labour but not to the weight of the baby. There was no significant difference between the amount of moulding measured on films taken during a contraction and that measured on films taken immediately after the contraction. The maximum amount of moulding occurred at full dilatation of the cervix. In 16 cases films were taken before the membranes ruptured and in all but one moulding was already present.

X-rays from another 1,000 cases, taken during labour for other purposes, were reviewed. In these patients the pelvis was normal and spontaneous delivery occurred. All but 15 showed the type of moulding described. In 15 cases there was a difference in level between the 2 parietal bones at the sagittal suture, this distance did not exceed 4 mm.

It is thought that moulding of the foetal head during normal labour is produced by pressure from soft tissues (probably the lower uterine segment) and not the bony pelvis. In cases of hypotonic inertia moulding is usually slight, whereas in 12 cases of hypertonic uterine inertia very marked moulding was seen.

Definite differences in moulding, from those described, were seen in cases of contracted pelvis studied by the same technique. These differences could be ascribed to direct pressure from the bony pelvis as the head attempted to negotiate the site of contraction. If the contracted part of the pelvis was successfully passed the abnormal moulding disappeared. The most striking pathological change in moulding was a difference between the levels of the two parietal bones at the sagittal suture. A difference of 5 mm. or more provided good confirmation of cephalo-pelvic disproportion. Pathological moulding was seen in pelves contracted at the brim and at the outlet.

It is suggested that tentorial tears can be accounted for by excessive normal or pathological moulding, either in the pelvis or as the head is crowned. The authors consider that study of the moulding of the foetal head, as seen on X-rays taken during labour, might be of value in establishing the presence of cephalo-pelvic disproportion.

Peter J. Huntingford

112. **Steroid Anaesthesia in Obstetrics and Gynaecology.** (Die Steroidnarkose in der Geburtshilfe und Gynäkologie.)

By H. K. Zinser and F. F. Bachmann. *Zbl. Gynäk.*, **80**, 1831–1841. Nov. 22, 1958. 1 fig. 1 table. 47 refs.

This is a report on Hydroxydion (H.), chemically allied to steroid hormones. It was developed after the discovery that progesterone, desoxycorticosterone and other steroids have hypnotic properties if given in large doses. H. has no hormonal effect but has a potent anaesthetic action. It is given by intravenous injection dissolved in warm saline. It is much less toxic than barbiturates. Respiratory depression is only observed with doses far above those required for anaesthetic purposes. Induction of anaesthesia is said to be smoother and more pleasant than with barbiturates. Muscle relaxation is such that intubation is often possible without the additional use of relaxants.

Post-operative vomiting and nausea are extremely rare.

Disadvantages of H. are a latent period of three to five minutes, and irritant effects, if injected outside the vein. Transplacental passage of the drug is either absent or minimal.

The authors report on a series of 62 obstetric and 136 gynaecological operations, during which H. was the main anaesthetic agent. When used for Caesarean section the newborn infant was usually more wakeful and more ready to cry than after other types of anaesthesia. In many cases other anaesthetic agents, particularly nitrous oxide, were used in combination with H. if relaxation, depth or duration of anaesthesia were inadequate. A liberal oxygen supply was given throughout. With a standard dose of 1 g. for patients of average weight, anaesthesia lasted about 30–40 minutes.

Barbiturates must not be used in combination with H. as they have a considerable potentiating effect which may lead to prolonged apnoea.

Bruce Eton

INFANT

113. **Staphylococcal Infection in a Maternity Hospital: Epidemiology and Control.**

By W. A. Gillespie, E. Simpson and R. C. Tozer. *Lancet*, **2**, 1075–1080. Nov. 22, 1958. 5 tables. 2 figs. 26 refs.

This investigation was carried out among full-time infants in the Bristol Maternity Hospital for more than 2½ years, with the objects of studying the sources and modes of spread of staphylococci among infants. The infants were cleaned up before leaving the labour ward but were not bathed until their umbilical cords separated on about the 7th day. The nurses wore masks, but not gowns, and washed their hands before and after handling each infant. Saline moistened swabs were taken from nose, umbilicus, skin of the groins, neck, perineum, axillae and popliteal fossae of the infants at regular intervals. Swabs were also taken from the noses and

hands of the nurses and from the noses of 245 mothers on admission. "Settle plates" were exposed in the nurseries and "sweep plates" cultures made from infants' blankets and garments. Swabs were taken from any open lesions obtained by the infants. It was found that most infants became staphylococcal carriers before they were two days old, the umbilicus usually being colonized first. There were differences in the persistence of staphylococci in the various carrier sites, nasal carriage usually persisting until discharge from hospital whereas the umbilicus and groin, which were usually colonized before the nose, often lost their staphylococci later. Sixty-nine per cent of the staphylococci isolated from infants were resistant to penicillin, 18 per cent were insensitive to streptomycin and 14 per cent to sulphonamide. This resistance appeared to be related to the therapeutic practice of the hospital at the time. It was considered that many staphylococci entered the nurseries via the noses of the nurses and other visitors but once introduced they spread from infant to infant without colonizing the noses of the nurses. The infants themselves were the most important immediate sources of infection and the handling of the infants by a common staff was an important means of transferring staphylococci from infant to infant. The mothers were not important sources of staphylococci in the nurseries. Staphylococcal lesions developed in 11·8 per cent of the infants mostly in the 2nd week of life. Infants who became heavy staphylococcal carriers by the 2nd day of life subsequently developed skin sepsis more often than others.

Three methods of reducing cross-infection were investigated. Disinfection of blankets and garments during laundering had no detectable effect on staphylococcal cross-infection or on the incidence of staphylococcal sepsis; the use of a disinfectant hand cream (Chlorhexidine cream) by nurses was accompanied by a moderate reduction in staphylococcal cross-infection among infants; the application of a disinfectant dusting powder (hexachlorophane) to the umbilical area of the infant caused a pronounced reduction in staphylococcal colonization of the umbilicus.

H. H. Fouracre Barns

114. A Staphylococcal Type-80 Epidemic in a Maternity Hospital.

By M. C. TIMBURY, J. S. WILSON, J. G. P. HUTCHINSON and A. D. T. GOVAN. *Lancet*, **2**, 1081–1084. Nov. 22, 1958. 4 tables. 9 refs.

The epidemic broke out in a maternity hospital with 120 beds divided into 3 separate units. The hospital has a sick nursery to which ill or premature babies from all three units are admitted and from which information about these infections was obtained. Mild infections due to *Staphylococcus aureus* were common in the sick nursery before the epidemic and were due to various types (but not type 80). Type 80 was first isolated on 19th November, 1957. Thereafter until the hospital closed 6 weeks later on 4th January, 1958, type 80 caused 14 of the 18 infections appearing in the sick nursery. There was a high case incidence of serious infections (9 out of the 18) and all were due to type 80. Five of the 9 babies with serious infections died. After closure of the hospital nasal swabs were taken from 475 members of the staff. Thirty-eight per cent were found to carry *Staphylococcus aureus* but only 0·6 per cent harboured the epidemic strain and these were regarded as victims of type 80 rather than its source. During the epidemic *Staphylococcus aureus* was isolated from the nose of 13 babies but only 3 were found to carry type 80. When the hospital was closed numerous sites were sampled for *Staphylococcus aureus* but type 80 was found only once in a communal blanket used during changes of infants' clothing—and this failure to isolate the epidemic strain was unexpected. By a follow up of babies delivered in the last 2 weeks of the epidemic it was discovered that 21 of 99 babies had developed infections at home. Twenty of these babies were visited about a month after their discharge from hospital and swabs taken from the lesions. Sixteen were due to *Staphylococcus aureus* but only 4 were due to type 80. Nasal swabs from these babies and their mothers showed that a high proportion were staphylococcal nasal carriers, but only 4 babies harboured type 80 and these were the same 4 babies who had infections due to type 80. Three mothers carried type 80 and in each case their baby was infected with the same strain. Nasal swabs taken 4 months after discharge from hospital showed that the number of staphylococcal nasal carriers among both babies and mothers was much lower. After closing the hospital, the whole building was thoroughly disinfected using a formaldehyde spray and all equipment sterilized. The hospital was reopened on 22nd January, 1958, and no infection due to type 80 appeared in the six months since its reopening. The authors observe that the strain of *Staphylococcus aureus* appeared quite suddenly as the predominant cause of infant infection and remained predominant until the hospital was closed. They consider it unlikely that it could have been eliminated by measures usually recommended, which are mostly aimed at preventing widespread colonization, because such did not occur.

H. H. Fouracre Barns

115. Delayed Positive Direct Coombs Test in a Healthy Rh-Positive Child of a Mother with Incomplete Rh-Antibodies. (Gesundes Rh-positives Kind mit verspätet positivem direkten Coombstest bei einer Mutter mit inkompleten Rh-Antikörpern.)

By M. MATTHES and O. PREISLER. *Zbl. Gynäk.*, **80**, 1957–1960. Dec. 13, 1958. 20 refs.

An Rh-negative patient was found to have incomplete Rh-antibodies for the first time in her second pregnancy at a titre of 1:32 and later of 1:8. The child, born shortly before the expected date, was Rh-positive, with a cord-blood haemoglobin of 19·5 g. and a negative direct Coombs test. The child's blood was investigated repeatedly. On the 11th day the haemoglobin was 17·4 g., the general condition and colour were good. On the 18th day, the direct Coombs test on venous blood

was positive for the first time at a titre of 1:64. At that time the maternal blood revealed an Rh-antibody at a titre of 1:256. The child remained well and did not require any special treatment.

The authors assume that minimal amounts of maternal antibodies must have passed the placental barrier during labour. Their affinity for erythrocytes was so feeble that at the time the cord blood was collected the antibody was not yet fixed on the red blood corpuscles.

[It would have been of interest to demonstrate the specificity of the antibody found on the child's red cells on the 18th day.]

Bruce Eton

116. **The Fetus of Multiple Gestations.**

By A. F. GUTTMACHER and S. G. KOHL. *Obstet. Gynec.*, **12**, 528–541. Nov. 1958. 16 tables. 1 fig. 25 refs.

The authors analyzed 1,327 twin deliveries which occurred between 1950 and 1956. They found that the median birth weight for a twin was 2,377 g. (5¼ pounds), approximately 650 g. less than a singleton of the same intra-uterine age. After the 35th week twins and singletons gain equal amounts. With twins, males are heavier than females, and twins from two eggs heavier than from one egg.

A vertex presentation is associated with the best salvage for both infants; both twins presented by the vertex in half the cases. The critical birth weight for twins so far as survival is concerned is 2,000 g.

The extra risk for second twins is mainly due to neonatal loss due to intra-uterine hypoxia following delivery of the first twin. Congenital malformations are twice as common in twins as in singletons.

J. G. Dumoulin

117. **Factors Influencing the Survival of Triplets.**

By G. R. KURTZ, L. L. DAVIS and J. B. LOFTUS. *Obstet. Gynec.*, **12**, 504–508. Nov. 1958. 3 tables. 4 refs.

A series of 21 triplet pregnancies had an overall foetal loss of 33 per cent. In 11, all 3 babies survived, and in 4, all 3 were lost. The main cause of foetal wastage was prematurity. The birth hazard for the second and third triplet was greater than that for the first.

Weight differences among babies of the same set had no appreciable effect on survival.

Results may be improved by: (*a*) better prenatal care with bed rest; (*b*) reduction of the interval between delivery of premature triplets; (*c*) elimination of elective internal podalic version and extraction for delivery of premature triplets; and (*d*) judicious and sparing use of anaesthetics.

J. G. Dumoulin

118. **Treatment of Scleroedema in the Newborn with Vitamin E.** (Die Behandlung des Sklerödem bei Neugeborenen mit Vitamin E.)

By H. WENIG and J. WESTPHAL. *Zbl. Gynäk.*, **80**, 1673–1677. Oct. 25, 1958. 4 figs. 10 refs.

In this condition there may be circumscribed areas of firm oedema in the thighs and calves of infants 2–3 days old. In severe cases most of the body is affected, usually with the exception of the soles of the feet, the palms and the genitalia. Slight oedema may be due to chilling of the body but the authors believe that the capillary damage may also be due to vitamin E deficiency.

They observed 26 cases of scleroedema amongst 2,655 infants born during the years 1956/57. Nineteen were males and 7 females. Only 5 of the children weighed 2,500 g. or less.

As suggested by Gerloczy the infants were treated with not more than 15 mg. of tocopherol by daily intramuscular injection. The resulting diuresis caused the oedema to disappear within 3–4 days.

In the course of their studies the authors observed a high level of daily urinary 17-ketosteroid excretion which dropped to normal values with subsidence of the oedema.

Bruce Eton

GYNAECOLOGY

119. **Culdoscopic Examination in Cases of Female Infertility.**

By P. LUNDSTRÖM. *Acta obstet. gynec. scand.*, **37**, 434–447. 1958. 3 figs. 29 refs.

In 63 out of 75 infertile women who were examined in the Umeå (Sweden) Hospital during 1954 to 1957 the last step in the examination was culdoscopy with simultaneous injection of 2 ml. of a 0·5 per cent indigo carmine solution through a uterine cannula. (In the remaining 12 cases culdoscopy could not be done because of pelvic peritonitis, long and narrow vaginas or faults in technique.) It is claimed that this method, in addition to avoiding the formation of oil granulomata and exposure of the ovaries to radiation, affords more detail than hysterosalpingography because the uterus, the oviducts, the ovaries and other pelvic structures can be directly inspected.

The average stay in hospital was 3·3 days. There were no complications apart from one injury to the rectum in a case of pelvic tuberculosis, and three cases of transient mild pyrexia. The findings were normal in 30 women, there were advanced lesions in 20, and intermediate findings in 13. Six out of the 75 patients later became pregnant; in 3 of them the findings had been normal, in 2 there had been slight changes, and the remaining patient had not been culdoscoped for technical reasons.

N. Alders

120. **The Local Use of Anti-inflammatory Hormones in the Treatment of Tubal Obstruction.** (Hormones antiphlogistiques in loco dans le traitement de l'obstruction tubaire.)

By A. DE MORAES and M. PEANO. *Gynéc. Obstét.*, **57**, 244–272. 1958. 3 tables. 10 figs. 61 refs.

In this series of 35 cases treated in the Institute of Gynaecology, University of Brazil in Rio de Janeiro, the

authors used antiphlogistic treatment in the broadest possible sense of the term. They emphasize that it is not simply anti-inflammatory treatment.

In cases of bilateral hydrosalpinx they used what they called their type III therapy consisting of oral hydrocortisone 0·04 g. per day for the first five days, followed by 0·03 g. per day for 15 days in the first menstrual cycle of the treatment and in the second and third cycles 0·02 g. per day. Dihydrostreptomycin 1 g. was instilled into the uterus with a hysterosalpingography introducer on five separate occasions between the 8th and 18th days of the second cycle. Similarly, dihydrostreptomycin 1 g. with hydrocortisone 0·025 g. was instilled 5 times in the third cycle.

In cases of simple ampullary block type II treatment similar to type I but with instillations with pressure maintained for 5 minutes in the first cycle was carried out.

In other cases they used the type I treatment which consists of Prednisone by mouth as well as local streptomycin and cortisone. The cases are very fully reported and the treatment really seems to vary from case to case.

Anyhow, it is claimed that the failure rate is only 11·4 per cent, the tubes being demonstrably open in 88·6 per cent of cases and pregnancy resulting in 71·4 per cent of cases.

[A parallel series of cases in this country might be worth trying—although chronic pelvic inflammatory disease seems to be very different in English patients from that found in Latin countries. For instance, it is much commoner at the French Hospital, London, than at other London hospitals.]

Elliot Philipp

121. **Tubo-Uterine Spasm.**

By B. C. MURLESS. *S. Afr. med. J.*, **32**, 1209–1211. Dec. 20, 1958. 3 figs. 7 refs.

The author describes a case in which a filling defect was demonstrated in the right cornu of the uterus. This defect was again demonstrated at a later date in a different radiological department. The left tube was not patent on the first occasion, but it was on the last. At no time was the right tube found to be patent. Examination under anaesthesia and curettage revealed no abnormality. Because of the very definite X-ray findings, laparotomy was performed and the uterus was incised anteriorly in the midline. No tumour, muscle defect or congenital abnormality could be observed in the cavity. The right tube appeared to be patent. The incidence and mechanism of spasm is discussed. It may sometimes be a cause of dyspareunia. The author feels that the frequency of conception following adoption and medical reassurance (which dispels mental anxiety) is due to the fact that spasm is relieved.

L. J. Abramowitz

122. **The Terminology and Classification of Congenital Ovarian Dysgenesis.** (Zur Terminologie und Einteilung des konnatalen ovariellen Dysmorphismus.)

By H.-H. STANGE. *Geburtsh. u. Frauenheilk.*, **18**, 1263–1267. Oct. 1958. 1 fig. 40 refs.

The gonads from 130 cases of gonadal dysgenesis, treated in the Gynaecological Department of the University of Kiel, were studied histologically. Using the histological and clinical features the author has divided these cases into 6 main morphological groups.

(1) Agonadism, characterized by complete absence of the gonads, although rudiments of the Müllerian or Wolffian systems may be present. The external genitalia are usually female. The chromosomal sex may be either male or female.

(2) Hypogonadism. The ovaries are rudimentary or hypoplastic. This group includes Turner's syndrome and the Bonnevie-Ullrich syndrome.

(3) Hypergonadism, in which the parenchyma of the ovary is hyperplastic and filled with primordial and primary follicles.

(4) Pseudo-hypergonadism, which is characterized by enlarged and sclero-cystic ovaries, due to stromal hyperplasia (Stein-Leventhal syndrome).

(5) Dysgonadism includes the Klinefelter syndrome.

(6) Ambigonadism. These are true hermaphrodites with either bilateral or unilateral ovo-testes, or an ovary on one side and a testis on the other.

Peter J. Huntingford

123. **The Diagnosis of Sex in Intersex and Ovarian Dysgenesis.** (Die Bedeutung des Geschlechtsdiagnostik für die kongenitale Intersexualität und ovariellen Fehlbildungen.)

By K. RUMPHORST. *Geburtsh. u. Frauenheilk.*, **18**, 1257–1262. Oct. 1958. 1 table. 1 fig. 27 refs.

The chromosomal sex has been determined of 121 cases of intersex and gonadal dysgenesis treated in the Gynaecological Department of the University of Kiel. In all cases the gonads had been removed and studied by serial section, so that the results of histological and chromosomal sex diagnosis could be compared.

The cases were classified into the groups suggested by Stange (see preceding abstract). In every case the chromosomal sex agreed with the histological findings. There were 2 cases of agonadism, 1 of which was male and the other female. Of 26 cases of hypogonadism 13 were female. Seventy-one patients with sclerocystic ovaries all had female sex chromatin. There were 6 female pseudohermaphrodites (adrenal origin) with female sex chromatin. Seven male pseudohermaphrodites with female external genitalia and 4 others with intersexual genitalia had testes and male sex chromatin. Of 3 patients with ambigonadism, with ovo-testes, 2 had female and the other had male sex chromatin.

It is possible to diagnose and classify the type of gonadal dysgenesis by determining the chromosomal sex without resorting to laparotomy or biopsy of the gonads.

Peter J. Huntingford

124. Testicular Feminizing Syndrome in Male Pseudohermaphrodite: Report of Two Cases in Identical Twins.

By H. K. MARSHALL and H. I. HARDER. *Obstet. Gynec.*, **12**, 284–293. Sept. 1958. 8 figs. 33 refs.

Two identical twins, who at one time were both airline stewardesses, are described. Both got married. Both were psychologically normal and normal-appearing "females" with female body habitus and fat deposits. Breast development was normal. Hair was absent on the face, scanty or absent in the axillae and pubis. External genitalia were normal. The vagina ended as a blind pouch and was underdeveloped. The internal female organs, that is uterus and tubes, were rudimentary. The gonads were undescended testes, consisting of seminiferous tubules without spermatogenesis, with a marked increase in interstitial Leydig cells. The appearance closely resembled undescended testes except that tubular adenomas were common. Bilateral excision of gonads and rudimentary internal female organs was carried out in both patients. Hormone assays suggested that both oestrogens and androgens were produced by the testes. Each patient was given oestrogen therapy.

J. G. Dumoulin

INFECTIONS OF THE REPRODUCTIVE ORGANS

125. Pelvic Abscess in Gynaecological Practice: A Clinical Analysis of 80 Consecutive Cases.

By H. J. H. CLAASSENS. *S. Afr. med. J.*, **32**, 1171–1175. Dec. 6, 1958. 2 tables. 1 fig. 18 refs.

The author reports on a series of 80 cases of pelvic abscess. Comparing the figures for Groote Schuur Hospital, Cape Town, for 1946 and 1956, it would appear that pelvic infection has decreased by a third in the European and the Bantu, but that the incidence has remained the same in the Cape Coloured group. In 42 cases (52·5 per cent) no obvious cause was found. In 38 cases it was related to childbirth, abortion, operative intervention, diverticulitis, appendicitis, old standing infection and investigations for infertility. In no case was gonococcal infection found to be the cause. Mixed organisms such as staphylococci, streptococci and *E. coli*. were cultured, and in 55 per cent of cases no growth was obtained. The most common symptoms were pain and dysuria. In 82·5 per cent of cases the menses were unchanged. Constipation and diarrhoea were not uncommon features. The important signs were tenderness and the presence of a mass in the abdomen and pelvis or only the latter. There was little or no correlation between the organisms cultured from the cervix and the abscess. The results of sedimentation rates and white blood counts were too equivocal to be of much value in the differential diagnosis. The diagnostic test is colpopuncture.

Apart from preventive treatment, in the established case the important measures are broad spectrum antibiotics, intravenous therapy in toxic cases and early colpopuncture. Chemotherapeutic "cover" is suggested for the next period, and patients should be seen at regular intervals to treat residual pathology. After 3 months they should be readmitted to exclude tuberculosis or appendicitis if the mass was right sided. Late surgery is sometimes indicated. There were 2 deaths, a mortality of 2·5 per cent.

L. J. Abramowitz

126. Typhoid Fever with Vulvovaginitis.

By D. W. T. ROBERTS and S. L. BARSON. *Lancet*, **2**, 1043–1044. Nov. 15, 1958. 1 fig. 17 refs.

The authors describe two cases of vulvovaginitis, one with vulval ulceration, associated with typhoid fever. In both cases the patients had recently been abroad and in both the genital condition preceded the diarrhoea or other symptoms of typhoid. The fact that in both cases the genital condition cleared up concurrently with the typhoid fever suggests a close association between the two conditions. The authors suggest that the spread of infection to the genital region is by embolism. They conclude that acute genital ulceration, the so-called Lipshütz ulcer, should be regarded as symptomatic of some general illness with enteric fever high on the list.

H. H. Fouracre Barns

127. Treatment of Chronic Inflammatory Diseases of the Genital Tract with Prednisone. (Über die Prednison-Behandlung chronisch-entzündlicher Genitalerkrankungen.)

By H.-J. STAEMMLER, *Zbl. Gynäk.*, **80**, 1655–1659. Oct. 18, 1958. 1 table. 22 refs.

The author reports on the results of treatment with oral prednisone in 150 patients suffering from chronic inflammatory conditions of the adnexa and parametrium. Five mg. of prednisone were given twice daily for two weeks and in about half the patients once daily for another 10 days.

In patients with palpable adnexal tumours regression was unequivocal in 50 per cent. Subsequent laparotomy revealed that in 6 cases failure of response to treatment was found to be due to an error in diagnosis.

The results were better in cases of chronic adnexitis without inflammatory swellings. In 4 cases of failure subsequent laparotomy showed long-standing thick fibrous adhesions.

Exacerbation of the inflammatory process was never observed as a result of treatment with prednisone.

Bruce Eton

128. Comparative Evaluation of Diagnostic Methods in Genital Tuberculosis. (Vergleichende Beurteilung der diagnostischen Methoden bei Genitaltuberkulose.)

By E. ABUREL, V. PETRESCU and H. CONGREA. *Zbl. Gynäk.*, **80**, 1508–1512. Sept. 20, 1958. 2 tables.

In a group of 80 patients suffering from genital tuberculosis the incidence of positive findings with various diagnostic methods was as follows: culture of menstrual blood of 74 patients (52·7 per cent); culture of endometrium of 80 patients (56·2 per cent); culture of cervical

secretion of 80 patients (28·75 per cent); culture of saline after uterine irrigation in 70 patients (31·4 per cent). The total yield of positive cultures amounted to 67·8 per cent. Histology gave positive findings in 71 per cent of 80 patients.

The advantage of histological examination is that the diagnosis can be made very quickly; its disadvantages are that it is not without risks; it is contra-indicated in some patients; it requires hospitalization.

With bacteriological methods there are no contra-indications and no risks; they can be used in out-patients and in large numbers; they can be repeated indefinitely; they can be used for control of patients undergoing treatment. Their main drawbacks are delay in diagnosis by 6–12 weeks and a slightly lower incidence of positive findings. However, the authors admit that in many cases an insufficient number of specimens were cultured.

Guinea-pig inoculation, radiological methods and exploratory laparotomy were not assessed in this series.

Bruce Eton

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

129. **White Lesions of the Vulva.**

By A. B. HYMAN and H. C. FALK. *Obstet. Gynec.*, **12,** 407–413. Oct. 1958. 1 ref.

Carcinoma in Situ of the Vulva.

By J. D. WOODRUFF and E. E. HILDEBRANDT. *Obstet. Gynec.*, **12,** 414–424. Oct. 1958. 1 table. 10 figs. 25 refs.

Paget's Disease of the Vulva.

By E. A. BIRGE, R. S. CRON and W. MADDEN. *Obstet. Gynec.*, **12,** 425–429. Oct. 1958. 3 figs. 17 refs.

The above 3 studies, all on allied vulval conditions, give an excellent résumé of the rather perplexing skin diseases seen in this region; such conditions as leukoplakia, lichenification, Bowen's disease, kraurosis, Paget's disease and carcinoma *in situ* are discussed. Histological features, treatment and prognosis, together with other outstanding features are all detailed, and the articles are recommended to those who are interested in the modern views on vulval skin pathology.

J. G. Dumoulin

130. **A Study of Epidemiologic Factors in Carcinoma of the Uterine Cervix.**

By E. G. JONES, I. MACDONALD and L. BRESLOW. *Amer. J. Obstet. Gynec.*, **76,** 1–10. July 1958. 17 tables. 10 refs.

This controlled study failed to provide any evidence that dietary deficiency, including thiamin and riboflavine, played any part in aetiology of cancer of the uterine cervix. Nor was there any difference in urinary excretion of oestrogens or in factors that might suggest deficiency in oestrogen metabolism such as mastodynia, time of onset of menarche or menopause, or irregularity of menses. When Jews were eliminated from the study it was found that circumcision or the lack of it was as frequent in the cancer cases as in the controls but the greater incidence of cancer in Gentiles was confirmed. Number of pregnancies, frequency of instrumental delivery, frequency of coitus or duration of marital state did not seem to play any part in aetiology. There were, however, lower standards of living, at least in early life, among the cancer cases, and a higher incidence of stressful conditions such as domestic insecurity and unstable marital relations. Early marriage and early first and last pregnancies were more frequent, suggesting early sexual maturation.

F. J. Browne

131. **Intra-epithelial Carcinoma of the Uterine Cervix.** (Il carcinoma del collo interno.)

By G. REMOTT. *Riv. Ostet. Ginec. prat.*, **40,** 4–57, Jan; 457–519, May; 784–833, Aug. 1958. 113 figs. 419 refs.

The author reviews the literature of intra-epithelial carcinoma during the past 50 years. He refers to his own material of approximately 2,000 cervical biopsies without specifying the number of instances of intra-epithelial carcinoma, carcinoma or other lesions. Though he considers clinical and therapeutic aspects, he concentrates on the problem of histological, histochemical and cytological diagnosis. From consideration of the literature and his own material, the author concludes that intra-epithelial carcinoma is an established entity and that histological examination is the only reliable method of diagnosis. [The figures are almost entirely reproductions from articles of other authors; the references are extensive.]

M. Caturani

132. **Current Treatment of Carcinoma of the Cervix.**

By H. L. KOTTMEIER. *Amer. J. Obstet. Gynec.*, **76,** 243–251. Aug. 1958. 1 table. 5 figs.

Though good results have been got by some operators in cancer of the cervix the price in complications is high and fistulae occur in 10 per cent of non-irradiated cases.

The results from primary radiotherapy seem to the author superior to those got by surgery. Though re-irradiation is of considerable value in suburethral metastases or tumours of the vaginal wall it is little use in persistent or recurrent cancer of the cervix or upper vagina if the case has been treated adequately the first time, and there is a definite place for radical hysterectomy, pelvic exenteration or extensive electro-endotherapy in the treatment of such cases. In the experience at Radium Hemmet there is no correlation between radiosensitivity and maturity of cancer cells, nor is the radiocurability in adenocarcinoma of the cervix worse than that in epidermoid cancer.

The first step in irradiation should be the intracavitary application of radium. Roentgen therapy as the first step is only indicated in far advanced cases and in large cauliflower tumours. The intra-uterine and vaginal radium application should be done with the best possible dosage distribution to the area to which it is felt that the

cancer extends. This requires a careful pelvic examination especially with regard to the extension of the growth, urography and sometimes venography which is useful in locating pelvic node metastases. The isodose curves should be worked out and be available at the time of application. The treatment time is determined by a direct reading of the dose in the posterior wall of the bladder and the anterior wall of the rectum. In the bladder the optimal dose is 5,500 and in the rectum 4,000 gamma r. The intracavitary application is divided into two treatments 3 weeks apart.

In cases of endocervical cancer or with spread to the paracervical tissue and pelvic node metastases an increase in the intra-uterine dose is desirable, preferably by an increase in the amount of radioactive material applied. Additional roentgen therapy is given to the pelvic wall from 2 anterior and 2 posterior portals in every case, and additional therapy is given to the area in the pelvis by telecobalt. Before this additional therapy a urovenogram is always required to give information on pelvic anatomy and the spread of the cancer.

In the three years 1949–1951, 1,081 patients were treated at Radium Hemmet. Treatment was refused by 11 patients and merely palliative treatment was given in 7·4 per cent. Radical hysterectomy was done on 43 cases of persistent or recurrent cancer and fulguration in 83. The 5-year apparent recovery rate is 89 per cent in Stage I; 64·4 per cent in Stage IIA; 45·2 per cent in IIB; 33·5 per cent in III; and 7·8 per cent in IV (invasion of bladder or rectum proved histologically or distant metastases present).

F. J. Browne

133. **Cervical Stump Lymphatics: An In Vivo Study.**

By E. EICHNER and L. RUBINSTEIN. *Obstet. Gynec.*, **12**, 521–527. Nov. 1958. 11 figs. 33 refs.

One malignant and 14 benign cervical stumps were injected with vital dye and operated on 3–6 days after injection. In 6 cases the dye pooled and did not spread, evidence of complete blockage of the lymphatics of the residual stump. In 5 patients the dye pattern was variable but followed irregular combinations of vesical, anorectal and vulval distribution. In the remainder, the spread was identical to that seen in the intact uterus and cervix. The degree and extent of spread was almost totally influenced by the scarring resultant from the previous pelvic disease and the previous operative procedure.

Scarring that destroys or limits the lymphatic drainage of the cervical stump is an important factor of the relative mildness of the malignant disease in some patients with true cervical stump carcinoma.

J. G. Dumoulin

134. **Cushing's Syndrome Associated with Adenocarcinoma of the Ovary.**

By V. PARSONS and B. RIGBY. *Lancet*, **2**, 992–994. Nov. 8, 1958. 2 figs. 15 refs.

The authors describe a case of adenocarcinoma of the ovary with ascites. At laparotomy a right ovarian mass was removed. Other secondary deposits were noted in the peritoneal cavity and the patient subsequently had deep X-ray therapy to the pelvis. Diabetes developed 3 days after operation and within a month of operation other evidence of Cushing's syndrome. The patient died four months later. The authors suggest that the stress of the malignant disease might have provoked hyperactivity of the adrenal sufficiently to produce Cushing's syndrome.

H. H. Fouracre Barns

OPERATIONS

135. **The Antithrombotic Activity of Butazolidin (Phenylbutazone).** (Hat Butazolidin antithrombotische Wirkungen?)

By H. STAMM. *Geburtsh. u. Frauenheilk.*, **18**, 1354–1361. Nov. 1958. 3 tables. 6 figs. 8 refs.

A trial was carried out in the Gynaecological Department of the University of Basel, in which phenylbutazone was used prophylactically for the treatment of phlebitis and thrombo-embolic complications in gynaecological and obstetric patients.

The incidence of phlebitis in gynaecological patients treated with phenylbutazone was 1·2 per cent compared with 4·2 per cent in those who received no treatment. The incidence of puerperal phlebitis was 1·7 per cent and 13 per cent respectively in the treated and control patients. There was no difference in the incidence of thrombo-embolic phenomena in the treated patients compared with the controls. Phenylbutazone relieved the pain of thrombo-phlebitis and febrile reactions were suppressed. The time for recovery was also slightly shortened.

The clinical trial was supplemented by *in vivo* and *in vitro* studies of the effects of phenylbutazone on the various clotting factors. No significant changes were found.

The author concludes that phenylbutazone acts only as an analgesic and antipyretic in relieving the symptoms of thrombo-phlebitis. He considers that it has no therapeutic value and recommends that it should not be used prophylactically, since by masking the symptoms of thrombosis the risks of embolism might be increased. Phenylbutazone should be used only for the symptomatic treatment of mild superficial phlebitis and thrombo-embolic complications should be treated with anti-coagulants.

[The details of the clinical trial are reported in *Schweiz. med. Wschr.*, 1957, **87**, 735.]

Peter J. Huntingford

136. **Results of Operative Treatment of Female Infertility.** (Unsere Ergebnisse mit der operativen Therapie der weiblichen Unfruchtbarkeit.)

By R. SLUNSKY. *Zbl. Gynäk.*, **80**, 1686–1694. Oct. 25, 1958. 3 tables. 47 refs.

The author reports on the results of surgical treatment for infertility in 50 women between 1946 and 1955. Only

33 women attended for follow-up examinations. Ventrisuspension alone, carried out in 3 women, resulted in one uterine pregnancy. Salpingolysis in 6 women was followed by 3 uterine pregnancies. Other plastic procedures on the uterine tubes (including partial resection) in 24 women yielded 2 tubal pregnancies and none in the uterus.

Patency tests carried out after operation on the tubes of 23 women showed occlusion within 2 weeks in 10, within 6 months in 5, within one year in 2 and later in 3 more.

Bruce Eton

137. **Pelvic Lymph Node Dissection Following Radiotherapy.**

By M. J. GRAY and R. GUTTMANN. *Amer. J. Obstet. Gynec.*, **76**, 629–633. Sept. 1958. 3 tables. 13 refs.

The renaissance of radical hysterectomy for cancer of the cervix in the past decade is largely due to the belief that radiation was defeated not only by radiation resistant tumours, but also by any cancer already established in the lymph nodes. It was suggested that the solution of the problem might be pelvic lymphadenectomy after completion of radiotherapy, and in 1943 Taussig reported 175 transperitoneal node dissections 2 weeks after radiotherapy with 26·8 per cent incidence of positive nodes. Of the patients with positive nodes 21 per cent survived 5 years and he credited the lymphadenectomy with a 10 to 15 per cent improvement in the results. Following Taussig's lead Morton operated on 103 patients, also by the transperitoneal route. He noted that the incidence of positive nodes was reduced from 30 to 16 per cent in the patients who had completed radiotherapy before operation. He had only 2 long term survivors among the patients with positive nodes and suggested that the place of pelvic node dissection remained to be established.

Gorton of Lund reported on 364 patients in whom extraperitoneal node dissection was done and noted a diminution in the incidence of positive nodes following radiation from 30 per cent to 14 per cent. He was convinced that the survival rate in Stages I and II cancer of the uterine cervix was improved 15 per cent by the addition of this operation to routine therapy.

In 1952 at the Sloane Hospital for Women and the Francis Delafield Hospital, New York, it was decided that all patients with Stages I and II cancer of the cervix who were to receive standard radiation treatment would have a routine extraperitoneal node dissection three months after completion of radiotherapy. From 1952 to 1956, 55 patients were so treated—28 in Stage I, 23 in Stage II, and 4 in Stage III. Of the 51 patients in Stages I and II only one (2 per cent) was found to have positive nodes after full radiotherapy, whereas the incidence of positive nodes in 61 patients who had radical hysterectomy as the primary method of treatment was 18 per cent. Of the 55 patients who had lymphadenectomy 20 had major post-operative complications including pelvic thrombophlebitis, leg oedema, and wound infection, and there was one death from pulmonary embolism. Twenty patients of the 55 are now alive and well; 13 have died of their original disease including all those with positive nodes.

The impression that radiotherapy was ineffective treatment for metastatic tumours in lymph nodes was formed in the years when external radiation delivered a far less than cancerocidal dose to the side wall of the pelvis. The authors' studies support the viewpoint that modern high voltage radiotherapy can effectively attack these nodes. The morbidity and mortality following pelvic node dissection after full radiotherapy provide a strong argument against this regime as a routine therapeutic measure, as does the paucity of positive nodes and the death of the patients with positive nodes despite node dissection.

F. J. Browne

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